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CLINICAL USE OF GONADOTROPIC SUBSTANCES IN WOMEN. I. TREATMENT OF SEXUAL IMMATURITY WITH CONCENTRATED PREPARATIONS FROM PREGNANCY URINE*

ELMER L. SEVRINGHAUS, M.D., AND MADELINE J. THORNTON, M.D.

From the Departments of Medicine and of Obstetrics and Gynecology, University of Wisconsin

MADISON

Since it is now understood that the anterior pituitary produces one or more materials which are essential in stimulating the development and function of the ovaries, a strictly rational substitution therapy in ovarian deficiencies would require the employment of anterior pituitary substance in demonstrably active form. No such preparation is commercially available. A material with similar activity, in animals, is fortunately available, however, from the urine of pregnant women. By means of this material it is possible to stimulate the development, maturation, and ovulation of the graafian follicles and the formation of the corpora lutea. The resemblance is imperfect when compared with repeated implants of pituitary tissue (1). These differences may be due to chemical differences between the true hormones and the substances excreted in the urine. Or extraneous material in the urine extracts may modify the action of any hormones present. Again, if the true hormones are present in urine extracts, differences in the proportions of follicle stimulating and luteinizing factors may account for variation between physiological results from use of pituitary or pregnant urine therapy. Since active standardized pituitary substance is not as yet available clinically, we have employed the urine extracts as furnishing undeniably pituitary-like properties—i.e., as the nearest approach to a source of pituitary material as yet to be had.

The extract which we have used as a rule has been "Follutein," for which grateful acknowledgment is hereby made to Dr. J. F. Anderson of the Biological Laboratories of E. R. Squibb & Sons. More recently some of the so-called "Antuitrin-S" has been placed at our disposal by Dr. E. A. Sharp of the Parke, Davis & Co. Laboratories.

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Our first approach to the use of follutein was in the treatment of cases with irregular, scanty, or absent menstrual periods. There are always a considerable number of such cases available through the Student Health Service at the University of Wisconsin. Cooperation of members of the staff of that service has placed several such young women under our care for this study. The other cases have come in connection with routine hospital and out-patient work of the Wisconsin General Hospital.

TABLE 1

AMENORRHEA AND OLIGOMENORRHEA
Treated with Anterior-Pituitary-like Substance from Urine

	Infantile Uterus	Uterus Normal Size, or Not Recorded
Cases, total	16	11
Amenorrhea	6	8
Oligomenorrhea	10	6
Menses very irregular	13	2
Obesity	6	6
Extract helped	6 + 3 (?)	4 + 1 (?)
Extract failed to help	2 + 3 (?)	4

These 27 patients may be grouped as those with an infantile uterus of which there are 16, and those with a normal sized uterus or with uterus of unknown size. The pelvic examination has been made in each case by one of the gynecological staff of the hospital, Dr. Harris, Dr. Campbell, or Dr. Thornton. In several cases there is no record of the size of the uterus because of obesity sufficient to interfere with adequate bi-manual examination, or because detailed pelvic examination of young patients was not made in some cases. This group of 11 patients without demonstrated infantile uterus comprises therefore those with amenorrhea, oligomenorrhea, and very irregular menses where no known pelvic or general disease was responsible for the complaint. For various reasons most of them appeared to be "pituitary" types. Only four of the 27 in the combined group had basal metabolic rates outside the limits accepted as normal in this hospital (2). These were 17, 20, 22, and 23 per cent below the average normal, but even these patients were obviously not typically hypothyroid in type. Three of these four had thyroid therapy with general clinical improvement but no relief from amenorrhea. The fourth had a variable basal rate, was not clinically hypothyroid, and gave no favorable response to the use of thyroid.

The frequency of obesity in this group is not as great as one would expect from the usual association of obesity and infantilism in discussions of this subject in the older clinical literature. Even when obesity was observed it could rarely be characterized by any uncommon distribution of fat deposits. The obesity usually yielded to dietetic management when there was reason to trust the cooperation of the patient. We employ diets

of around 1200 calories for his purpose. It was often apparent that the rate of weight loss was disappointingly slow in such women, as compared with uncomplicated obesity based on overindulgence in food in patients with no signs of endocrine disturbances. The significance of the obesity and the slow loss in these cases is not clear.

The therapeutic plan with the use of the urine extracts was to give five daily hypodermic injections of 1.0 cc. each for the first five days after the cessation of each menstrual period. This timing was chosen as simulating the normal time when the pituitary stimulation to the ovary is expected. When no menses were present to fix a time, treatment was given at intervals of four weeks, five days at a time. The occurrence of menses served to determine a shift in this timing if subsequently necessary. The duration of the treatment was probably too short. Too little rather than too much treatment is advisable since these urine extracts are known to contain factors which stimulate luteinization and which may cause the formation of atretic follicles. By using limited amounts for a short time, early in the monthly cycle, the risk of causing undue atresia or luteinization might be avoided, although at the expense of failing to get positive results.

The only local reactions to the use of this material have been redness, tenderness, pain and swelling, but with no indication of infection nor of allergy. These reactions subside in 12 to 48 hours, without treatment. They tend to become less marked in successive periods of using the material. Affected areas are similar whether "Follutein" or "Antuitrin-S" is the agent used. Recent lots of follutein have caused less marked reactions, suggesting improvement in the purity of the material. On beginning a second course of treatment after a four-weeks' interval careful trial of only 0.1 cc. was made in the first few patients. No anaphylactic response was seen, and none has followed the use of the larger doses. A few patients had a fever for a few hours after injection, but this was not constant in the same patients and it is seldom seen. No other general manifestations have been observed.

The results of the therapy are not extremely reassuring, although in the group of infantile cases six patients have had what seems undoubted help in the re-establishment of a more regular flow of increased volume. A few cases are recorded as questionable since the results cover too few months to be dependable. Failure is recorded when two to four courses of treatment have shown no result. It is possible that with longer use of the material, or with larger doses these patients may respond. The results convince us that the material we have used is active in stimulating menstruation. They give reason to believe that the dosage is not yet adapted to individual needs. Larger doses we would still employ with caution and only after trying these moderate doses. Overdosage has been apparent in two patients where menorrhagia has followed promptly after the use of the first course of treatment. This lasted for one menstrual period only.

Several of these patients have more recently been treated with a combination of follutein, administered as above described, and a special anterior pituitary extract furnished by the laboratories of E. R. Squibb & Sons. This latter material is standardized by its growth-promoting ability on animals. The combination with follutein of this growth-promoting factor is based on suggestions from the reports of Evans, Meyer and Simpson (1), and of Morrell (3). The extract has been given hypodermically in 0.5 cc. doses on alternate days. Only two of those patients reported in this study have been under this combined treatment long enough to detect any results. They have shown apparently more progress than on the previous periods with the use of follutein alone. One, aged 14, with the most nearly typical Froehlich syndrome in the group, has had a rather copious menstrual flow after an amenorrheic interval of 13 months. Following two months of the combined injections she has grown 0.75 inch, although losing weight on a 1200-calorie diet. During the preceding six months she had grown 1.0 inch. These results are too recent to be more than an indication of greater activity when both the follutein, from pregnant urine, and a genuine anterior pituitary extract are combined. We anticipate even more definite results with gonad stimulating material derived entirely from the pituitary gland, which will be placed in clinical trial with these and further cases.

As a corollary of this study we have observed 14 women with excessive hair on the face, arms, legs or torso. The results of the use of pituitary treatment for alopecia were mentioned by Bengtson (4) last year, with some enthusiasm for the stimulation of hair growth by the extracts he used. Before we knew of Bengtson's work, an attempt to produce just the opposite type of result, i.e., the modifying of excessive hair-growth by the use of pituitary factors, was suggested to us by the rough clinical association between pituitary types and hirsuties in women. The possibility that adrenal and other factors are involved in the latter condition is, of course, not forgotten.

TABLE 2

HIRSUTE WOMEN

Treated with Anterior-Pituitary-like Substance from Urine

	Cases	Courses of Extract Given
Infantile uterus	6	0, 1, 3, 4, 6, 8
Infantilism (??)	5	2, 2, 3, 4, 10
Cystic ovary	3	1, 2, 3
(6 were obese)		

Most of these 14 patients were being treated because of infantilism or menstrual disturbances. Three were treated primarily because of the excessive hair, although the menses were not remarkable. In none of these

patients has there been any evidence that the rate of hair growth has been retarded or accelerated in the least. Three patients with cystic ovaries were given intravenous injections of a special "luteinizing" fraction of Follutein (to be described later), but with similar negative results. These patients include several with definite positive help from the therapy so far as the effect on menses is concerned. It is concluded that no certain effect on hair growth is to be expected from the pituitary-like materials in pregnant urine within the time and with the dosages with which these cases were treated.

SUMMARY

Treatment was given to 23 women who had been demonstrated to be sexually infantile, or had had long periods of amenorrhea or oligomenorrhea. Concentrated preparations from human pregnancy urine (Follutein and Antuitrin-S) were found to stimulate at least 10 patients to more regular and copious menstruation. Results were doubtful in seven, negative in six others. Hirsutism in 14 of these women was not relieved.

Addendum. Since submitting the above manuscript several patients who received these gonadotropic substances have had marked local and general reactions, temporary but definite enough to merit attention. General symptoms included fever, chills, nausea, back, pelvic and leg pains.

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PITUITARY CACHEXIA

REPORT OF A PATIENT TREATED WITH ANTERIOR PITUITARY EXTRACT*

JOHN C. BROUGHER, M.D.
VANCOUVER, WASH.

E. S., a white male, aged 63, was seen in his home, January 26, 1931. The chief complaints were: weakness, loss of weight, stomach trouble, attacks of nausea, gaseous eructations, extreme weakness and loss of axillary and pubic hair.

History of Chief Complaint: The patient had been well up to 1918, at which time he had had the influenza. Previous to this illness he had been doing hard ranch work. He could lift 200 pounds and work long hours. In 1913 he weighed 163 pounds. Before this illness he weighed 148-156 pounds. In 1923 he began to lose weight and in 1929 began having nausea and vomiting. Since March, 1931, he has had attacks of dyspnoea and asthmatic breathing. He had a vomiting spell in November, 1929, that lasted two days, and in January, 1930, one that lasted one week. The third attack began February 26, 1930. He has had several attacks since then. The most recent gastrointestinal upset was two or three weeks ago. The first symptom that alarmed the patient was weakness which he noticed while stacking hay, July, 1923. In 1927 he began to lose his axillary and pubic hair. The pubic hair disappeared first and he was not conscious of it until it was entirely absent. He began to lose his scalp hair in December, 1930, following an attack of influenza. He claims that the testicles diminished in size since having the mumps in 1902, but that they had become much smaller since the pubic and axillary hair began to diminish in 1927.

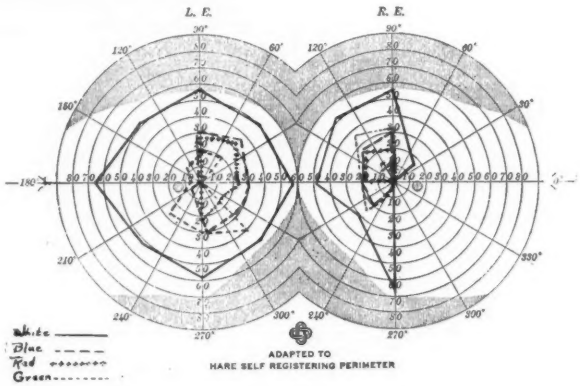
Past History: The patient had a fractured clavicle in 1924. He has had no operations. The past diseases include mumps, pertussis, diphtheria, influenza, measles, rheumatism and pleurisy. His general health had been good up until 1923. He had had sick headaches as a child up to the age of 15 or 16. He had noticed an impairment of vision, especially in the right eye, since 1927. His appetite was good except during gastro-intestinal disturbances consisting of gaseous eructations, nausea and emesis. There was no dyspnoea on exertion. The ankles swelled occasionally. Venereal disease was denied. Nocturia was reported (two or three times a night). There had been sexual impotence since 1923. He stated that the testicles seemed to be getting smaller. The legs were stiff at times. The patient worried very little, was not nervous and had a slow, steady gait.

*The Anterior Pituitary Extract (Antuitrin) was kindly supplied by Parke, Davis & Co.

Personal History: The patient sleeps well as a rule. His recreation is limited, but he walks as much as his strength permits. He drinks tea but not coffee, and uses no liquor, tobacco or drugs.

Family History: The father was drowned, and the mother died at 74 years of age. Three brothers are dead. One died in infancy, one from tuberculosis, and the cause of death in the other is unknown. Four sisters are alive and well; two died in infancy.

Physical Examination: The patient is very thin and walks very slowly and cautiously but does not shake or tremble. There is no scalp nor sinus tenderness. The pupils are equal and react to light and accommodation. There is a marked arcus senilis of each eye. The pupils are quite large. The temporal range of vision of the right eye is much diminished. The field of vision, as determined by Dr. H. L. Underwood, is illustrated on the accompanying perimeter chart (Fig. 1).



The ophthalmoscopic examination revealed a bilateral primary optic atrophy. The septum is deviated to the left so that an applicator could not be passed beyond the middle turbinate. The teeth are replaced by false plates. The throat, neck and chest are normal. The heart shows bradycardia. The pulse rate is 60, and the blood pressure 110/90. The lungs are clear. In the supine portion the abdomen is about level with the chest. The abdominal aorta is easily palpable. There are no areas of tenderness or palpable masses. The muscles of the abdominal wall seem rather soft and doughy. The penis is very small, and measures 7 centimeters in length. The left testicle measures 2 centimeters and the right testicle 2½ centimeters in length. Both testicles are very small and soft. The rectal and neuro-muscular examinations gave normal findings. The skin is dry and has rather a thickened feeling.

Laboratory Findings: The blood—hemoglobin was 56 per cent; coagulation time, 1 minute; the blood cell count was: red, 3,744,000; white, 4,550; polymorphonuclear, 43 per cent; small lymphocytes, 33 per cent.

The urine was yellow in color, cloudy and alkaline, the specific gravity was 1016. There was no albumin nor sugar present. The blood sugar, January 26, 1931, showed 74 mgm. per 100 cc. of whole blood. The basal metabolic rate, April 4, 1932, was minus 40. The glucose tolerance test, April 4, 1932, gave a fasting blood sugar of 91 mgm. sugar per 100 cc. of whole blood. Fifty grams of glucose was given orally. Thirty minutes later there was 158 mgm. sugar per 100 cc. of whole blood; one hour later, 130 mgm.; two hours later, 124 mgm. This resembles the curve of mild diabetes. A modified Mosenthal test gave normal findings. Blood and spinal Wassermann tests were normal.

Goetsch Test	Blood Pressure	Pulse	Respiration
	110/88	64	16
	108/88	..	..
	Adrenaline given—0.5 c.c.		
2½ min.	110/88	60	16
2½ min.	115/90	64	16
2½ min.	115/92	64	16
2½ min.	108/90	60	15
2½ min.	104/88	64	16
5 min.	112/86	60	16
10 min.	145/90	60	18
10 min.	140/90	66	16
10 min.	140/90	62	18
10 min.	134/90	72	18
10 min.	128/86	74	17
10 min.	125/80	64	16
10 min.	112/82	60	15

Roentgenological Report: A lateral view of the skull showed a pressure destructive deformity of the sella turcica, especially of the posterior clinoid process (Fig. 2). Changes shown in the sella turcica give evidence of a long standing, slowly developing tumor mass. (Report by Dr. Wallace E. Howarth, Portland, Oregon). Views of the forearm gave no evidence of bone disease except slight demineralization. There was a small spur on the lower end of the ulna. A roentgen examination of the chest and gastro-intestinal tract showed no abnormalities.

Progress of the Case: When first seen the patient was having a spell of emesis, and was extremely weak and prostrated. He was dyspnoeic and the heart rate was about 42. He was pale but not cyanotic. Because of his loss of weight, icteroid color of skin, weakness and vomiting, a carcinoma of the stomach was suspected, but after going into the history it seemed that many of his symptoms resembled those of Addison's disease; however the Goetsch test and a lack of deep pigmentation did not favor such a diagnosis.

Because of the extreme slowness of the pulse, it being never more than 45, the patient was given desiccated thyroid. Although he gradually gained in strength and his appetite increased, he still remained in bed most of the time and had a gastro-intestinal upset about every three or

four weeks. Occasionally, instead of the gastro-intestinal upset, he had an attack of what seemed to be bronchial asthma with severe dyspnoea and wheezing.

FIGURE 2

Not until after reading a case report of pituitary cachexia by Calder (1) did I suspect that this patient might have a pituitary disturbance. Because of these pituitary deficiency symptoms, the patient was given anterior pituitary extract. Treatment began in May, 1932, with injections twice weekly of 1 cc. antuitrin subcutaneously. Within two weeks the patient began to improve, and after 18 injections he was considerably stronger, had a better appetite and was more active. He was able to walk down town and back, a distance of about two miles, for the first time in three years.

On June 10, 1932, his glucose tolerance and basal metabolic rate tests were repeated. There was a little more sustained blood sugar curve than previously. The fasting blood sugar was 90 mgm. of sugar per 100 cc. of whole blood. Glucose (50 grams) was given orally. Thirty minutes later the glycemia was 154 mgm. per 100 cc. of whole blood; one hour later it was 150 mgm. and two hours later, 132 mgm. His basal rate was minus 15.

This case history, x-ray and perimeter findings were examined by Dr. A. J. McLean, and from the findings reported he considered the cachexia due to a chromophobe adenoma of the pituitary gland. Dr. McLean dis-

cusses this type of pituitary tumors in his article Chiasmal Syndromes (2).

SUMMARY

The case of a white male, aged 63, having symptoms of anterior pituitary lobe deficiency is reported. His basal metabolic rate was —40 and his glucose tolerance curve resembled that of mild diabetes. A positive Goetsch test and the absence of deep pigmentation militated against a diagnosis of Addison's disease. Enlargement of the sella turcica added to a rather typical clinical syndrome of weakness, anorexia, gastro-intestinal upsets, asthmatic attacks, loss of weight, low basal metabolic rate, loss of sexual power and libido, falling of axillary and pubic hair, low blood pressure and subnormal temperature makes fairly safe a diagnosis of pituitary cachexia. The patient was treated with anterior pituitary lobe extract, 1 cc. subcutaneously, twice weekly. This was followed by very definite improvement.

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MENOPAUSAL EPILEPSY

REPORT OF A CASE

ROBERT L. SCHAEFER, M.D.
AND
WILLIAM L. BROSIUS, M.D.
DETROIT

The etiology, pathology and causal factors concerned in the syndrome of epilepsy are far from solution. Genotypic influence, toxic causes, metabolic disturbances, endocrine dysfunction and cerebral vascular changes, no doubt, are all contributory. As a result of this chaos it is necessary that each case be treated as an individual and the separate contributory factors be determined.

Souques and Gilbrin (1) in three cases found an alteration or definite association of attacks with the menstrual cycle. Banus (2), in a study of six thousand cases, found that in one hundred ninety-six the attacks were considerably changed and some even initiated during the menopause.

This case is presented not because of its rarity and duration of observance, but mainly because of its response to specific endocrine therapy. The resultant therapeutic benefit, too, closely followed the final evolvement of the female sex hormone by Allen and Doisy. No response was obtained from the non-specific watery extract of the various ovarian substances, but with "Theelin" the therapeutic response was prompt and complete. Withdrawal of this substance produced a recurrence of the attacks.

Case No. 167. Female. Age, 48 years. Occupation, housewife. June 2, 1926.

History. Chief Complaint: About six weeks ago the patient retired at 10 p.m. feeling perfectly well. At 6:00 a.m. the following morning she went into generalized clonic convulsions, with foaming at the mouth, cyanosis, and biting of the tongue. She had four such convulsions that same day. Between convulsions she would fall asleep and lose all memory of her preceding convulsion. Her only aural symptoms were a headache associated with slight vertigo. The vertigo preceded the convulsions by one to two minutes. For the past year she had experienced occasional attacks of hot flashes. Six months prior to her convulsions there was a complete cessation of menstruation. No further convulsions were had until ten days after the first. One week after her first convulsion and two days after her last convulsion she had a menstrual flow lasting four or five days. She has had none since.

Past: The patient had typhoid fever at the age of nineteen and pneumonia at eighteen.

Personal: Her teeth were all extracted ten years ago. She complains of slight dyspnea after moderate exercise. Her habits are regular, and she has always enjoyed an excellent appetite. She eats a general mixed diet, and her bowels are regular. She sleeps well. During the past four or five years she has gained twenty-five pounds.

Gynecological: The onset of menstruation was at sixteen years, and her periods have always been regular with a twenty-eight-day interval, four days' duration, and normal flow. There has been no premenstrual or menstrual dis-

comfort. Menstruation ceased six months previous to her present illness. She has had six children, five of whom are living. One child died of measles.

Examination. General: There is a moderate obesity present of girdle type. There are no subthyroid findings.

Regional—Eyes: The pupils are irregular. The right is elliptic, although both react well to light and accommodation. Ophthalmoscopically the vessels appear normal and the discs are easily outlined. *Ears* and *Mouth* are normal, as are *Throat* and *Chest. Heart:* The relative cardiac dullness is 12 cm. to the left, none to the right of the sternal border. The heart sounds are normal. Her pulse is 64. Blood pressure: systolic, 140; diastolic, 70. *Abdomen:* Normal. *Extremities:* There are a few varicosed veins. *Neurological:* There is no edema. The tendon reflexes and skin reflexes are all normal and sensation is unimpaired. There is no muscle imbalance. *Special Eye Examination:* An eye ground examination was made by Dr. Thomas F. Keating and no abnormalities noted. *Special Neurological Examination:* This patient was referred to our office after Dr. H. F. Reye had completed an extensive neurological examination. Nothing significantly abnormal was found in the nervous system.

Laboratory: The urinalysis findings were normal. The complete blood count was within normal limits. Nonprotein nitrogen, creatinin, and blood sugar determinations were within normal limits. Kidney function dye test was normal. The basal metabolic rate was minus twelve and minus fifteen per cent.

Treatment: Desiccated thyroid gland, grains one-half, twice daily, was prescribed. Ovarian substance, 2 cc. was given intramuscularly twice each week.

Course: March 9, 1931. This treatment did not alter the course of the patient's convulsions in any appreciable degree. She had a seizure every seven or eight weeks and would have to remain in bed from one to two days after every attack. There would be an associated loss of memory for two to three days following the attack. The convulsions have been as described. Her treatment has been irregular. She still has occasional hot flashes. There has been a loss of twenty pounds in weight and a slight increase in her blood pressure which is now 165 systolic and 95 diastolic. At this time theelin, 2 cc., intramuscularly, was advised to be given two or three times a week.

December 1, 1931. In the ten months since treatment with theelin was instituted the patient has had only two attacks, and these were mild. These attacks occurred when there had been a lapse in treatment of four to five weeks.

April, 1932. She has had an average of two injections of theelin each week, and there have been no seizures for more than six months.

DISCUSSION

The work of Zondek, Kurzrock and Frank prove, by the chemical analysis of blood and urine, that very often an incretory imbalance is present during the menopause. Zondek states that at this time there is an excess of the pituitary sex hormone. Kurzrock's work tends to show that there is a lack of theelin, or the female sex hormone, and that when this lack of theelin is demonstrated its administration will produce excellent therapeutic results. Also, that if the urinary content of the female sex hormone is within normal limits the therapeutic administration will be of no benefit, or may even tend to aggravate the symptomatology of the menopause. It can be assumed, then, that the above case is one in which a lack of female sex hormone precipitated attacks with the clinical appearance of true epilepsy. It can also be assumed that replacement of this hormonic deficiency brought about a good therapeutic result. With the simplification and general use of these blood and urinary analyses for hormonic content the diagnostic and specific therapeutic field should be greatly widened.

SUMMARY

A case is presented in which attacks with the clinical appearance of true epilepsy appeared six months after cessation of menstruation at the age of forty-eight years. Gland extracts were used for five years without relief. Theelin has completely relieved the attacks.

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THE TREATMENT OF CLINICAL TETANY WITH IRRADIATED ERGOSTEROL*

C. I. REED, Ph.D., and LINDON SEED, M.D.
Departments of Physiology and of Surgery,
University of Illinois, College of Medicine
CHICAGO

It is the purpose of this paper to report the results of treatment with irradiated ergosterol of a number of patients suffering from postoperative parathyroid tetany. The literature on the experimental investigation of the relation of vitamin D in some form to the function of the parathyroids has been reviewed extensively by others [Moritz (1), Bloch and Faber (2), Grant and Gates (3), Higgins and Sheard (4), Hess and Lewis (5), Hess, Weinstock and Rivkin (6), Jones (7), Jones, Rapoport and Hodes (8), Brougher (9), Wade (10), Greenwald and Gross (11), Bauer, Marble and Claflin (12), Gleich and Goodman (13), Stern (14), Jaques (15), Findley (16), Hansmann (17), Pappenheimer (18), Shelling (19), Spies, Wilson and Strinkham (20), Taylor, Weld, Branion and Kay (21), Sjöstrom (22), Laurens (23), Thomson and Collip (24) and others]. It is, therefore, not necessary at present to enter into any further extensive discussion of the literature.

With the demonstration of successful intravenous administration of viosterol by Reed and Thacker (25), an attempt was made to administer it by this method to a case of postoperative tetany, the results of which were reported in brief two years ago (Seed and Reed, 26). In addition to this one a number of additional cases have since been treated.

The preparation used was viosterol 10,000 X, which is a solution in oil. The question of the danger of emboli from intravenous injection of the oil has frequently been raised. In more than 1000 injections of viosterol or of corn oil alone in amounts up to 15 cc., in dogs and human subjects, since this method was first adopted in February, 1929, we have never had any evidence of results that could be attributed to emboli. While we are still of the opinion that this substance is, in varying degrees, more effective when administered intravenously than by mouth, we have since discontinued the earlier method in case of human subjects, mainly because the patients themselves objected to the method, but also because in some cases the medication was done under home conditions and it was, therefore, impractical to give it by injection.

CASE REPORTS

Case 1. Mrs. H. H. Age, 56 years. An enlarged thyroid was present for seven years, with symptoms of thyrotoxicosis during the last two years, such as

*The expenses of this investigation were borne in part by grants from the American Academy of Arts and Sciences, from the Phi Rho Sigma Medical Fraternity, from Mead Johnson and Company, and from the Graduate School Research Fund, University of Illinois. The viosterol was supplied by Mead Johnston and Company.

extreme nervousness and chorea-like tremors. The basal metabolic rate was not determined. A subtotal thyroidectomy was done on March 28, 1930. Three days later occurred generalized tetanic seizures with laryngospasm. During the next two days the patient received hourly 4 gm. of Ca lactate by mouth and 3 intravenous injections, each of 5 cc. of 10 per cent $CaCl_2$. During the next eight days she received 1 cc. of parathormone daily. At this time she was discharged from the hospital. She continued on a regime of 12 gm. of Ca lactate daily, supplemented by 20 units of parathormone one to three times weekly, until July 23, when she was readmitted to the hospital in severe tetany with marked laryngospasm. The blood calcium concentration was 8.10 mgm. per 100 cc. The Ca lactate dosage was continued but the parathormone was increased to 1 cc. daily. After three weeks she was discharged as symptom-free.

During the next three months there were periods of freedom from tetany when the lactate treatment was supplemented with parathormone but never with lactate alone. But even in these periods she was not in normal condition. Also, she became progressively less responsive to both forms of treatment. On November 13, when she was readmitted to the hospital under our observation, she required approximately 115 gm. daily of Ca lactate. At this time she was almost constantly hysterical. She left the hospital on December 30, 1930, and while never since under observation, she is reported well and active. The treatment during this last period is detailed in the following table:

	Ca	P	
Nov. 18	6.38	3.92	
Nov. 21	....	....	0.5 cc. 8000 X viosterol i.v.
Nov. 22	7.76	4.08	
Nov. 23–25 inc.	....	....	20 gm. Ca lactate by mouth
Nov. 25	7.05	3.98	0.5 cc. viosterol i.v. Severe tetany
Nov. 26	8.69	....	0.5 cc. viosterol i.v.
Nov. 28	12.24	6.56	0.5 cc. viosterol i.v.
Nov. 29	....	....	0.5 cc. viosterol i.v. Total 2.5 cc.
Dec. 1	10.08	5.30	
Dec. 5	*7.41	5.03	Hysterical attack
Dec. 8	9.97	5.19	
Dec. 9	....	....	1 cc. viosterol by mouth
Dec. 10	....	....	1 cc. viosterol plus 0.5 cc. i.v., fasting
Dec 11	....	....	1 cc. by mouth
Dec. 12	8.88	6.92	1 cc. viosterol by mouth
Dec. 13–16	....	....	1 cc. daily. Total 8 cc.
Dec. 17	8.97	4.96	
Dec. 18	12.30	....	

*The end point in the titration was indefinite, which renders this determination of doubtful significance.

One of the most striking things in this case was the early alleviation of hysterical tendencies as manifested not only by behavior but by appearance of the facies. It will be noted that the patient had required progressively increasing amounts of Ca lactate and that no lactate was given after November 25. Nevertheless, she was able to absorb enough Ca from the normal food content finally to restore the blood Ca to a high level. The fact that for more than two years the patient has been symptom-free with no treatment suggests that this is a case of latent tetany and also that she might have reached this stage without viosterol. These possibilities are freely admitted. Nevertheless the early development of severe symptoms and the degree of refractoriness to all conventional treatment, together with the early response, and the degree of response to viosterol, makes it apparent that the development of latent tetany was materially hastened by the treatment.

This case also illustrates another point, i.e., the stabilization of the subjective symptoms. Both Ca lactate and parathormone to some extent re-

lieved her of tetany, but neither on the combination of both of these nor on either one alone did she feel and behave in a normal manner. On viosterol alone, however, there was a stabilization not easily defined but so apparent to an observer that it could scarcely be ascribed to malingering. All hysterical manifestations ceased promptly, except for one attack on December 5, in the interval between the two periods of treatment, although she did not at first know the nature of the injection. Injection of $CaCl_2$ never produced this result.

While Jacques (15), Findley (16) and others have failed to accomplish any benefit from administration of irradiated ergosterol, it is probable that they did not use a sufficiently potent dosage. It has been pointed out repeatedly that, in any form of deficiency of Ca-P metabolism, there is increased resistance to the toxic action of irradiated ergosterol. Furthermore, the early symptoms are easily recognizable, slowly developing, and on first appearance administration may be discontinued. Still further, the early effects are entirely recovered from. In view of these facts, then, it appears that dosages of high potency may be administered with safety under careful observation.

This first case also illustrates the relative value of the two routes of administration. A total of 2.5 cc. intravenously produced hypercalcemia comparable to that produced by 8 cc. by mouth, although it is apparent that the initial calcemia for the latter period was somewhat higher than that for the first period.

Case 2. Mrs. F. H. Age, 38 years. In February, 1928, a thyroidectomy was done for exophthalmic goiter, with "immediate" development of severe symptoms of tetany such as a positive Chvostek's reaction, twitching of facial muscles, weakness, burning tongue and numbness of the hands. No treatment was instituted. Later there was generalized epidermal desquamation and loss of the nails and hair. Three months later, according to the patient's own statement, a psychosis began to be manifest and she was then placed on calcium and parathormone therapy, the details of which are not known. This treatment was continued until January 27, 1929, before a blood calcium determination was made. On this date the concentration was 6.72 mgm. per 100 cc. During the next ten months calcemia fluctuated between this concentration and 8.72 mgm.

It will be noted that during the first two days of viosterol administration there was no subjective improvement, even with Ca lactate. But with a single large dose intravenously and without Ca lactate there was prompt improvement. To what extent this represents a combined or cumulative effect cannot be stated, but it is believed, in the light of subsequent experience, that a considerable part of the result must be assigned to a cumulative effect. At any rate this one period of administration maintained the patient symptom-free for a month, after which occasional small doses were sufficient to maintain her in good condition. The latter part of May, 1931, heavy medication by mouth was begun. Four such periods were completed between May and September. On September 29 her blood calcium was 17.05. It is probable that it was much higher in the interval since the last dose of viosterol. She now began to take Ca lactate occasionally, as symptoms demanded.

TABLE 2

	Ca	P	
Dec. 11, 1930	6.92	....	Mild symptoms of tetany. 12 gm. Ca lactate daily. 0.5 cc. 10,000 X viosterol by mouth.
Dec. 13	....	..	No improvement. Lactate discontinued. 0.8 cc. viosterol i.v.
Dec. 23	14.00	4.90	Felt better than for years. 0.5 cc. viosterol i.v.
Dec. 27	10.70	4.54	
Jan. 3, 1931	11.60	6.02	"Feels fine."
Jan. 8	13.80	....	Anorexia, otherwise feels well.
Jan. 14	....	....	Menses 14th to 17th.
Jan. 15	11.13	....	Slight burning and twitching about eyes and tongue.
Jan. 17	10.34	....	Some mild symptoms during menses. Took some Ca because of them. 0.4 cc. viosterol i.v. "Feels perfect."
Jan. 24	11.23	6.95	"Feels perfect."
Feb. 7	9.52	4.94	Menses, mild tetanic symptoms. 0.5 cc. viosterol i.v.
Feb. 16	6.63	12.13	Burning tongue, nervous, insomnia.
Feb. 21	7.38	6.05	
Mar. 6	9.99	4.91	
April 4	7.25	11.10	Menses due. Burning tongue. 0.5 cc. viosterol i.v.
April 7	9.20	7.62	Slight twitching of eyes last few days.
May 31	....	....	Began taking 0.3 cc. daily 10,000 X viosterol by mouth.
June 6	10.30	4.24	Just finished 2 cc. over 7 days.
June 24	....	....	0.5 cc. 10,000 X daily for 10 days by mouth. Symptom free.
July 4	....	....	Symptom free.
Aug. 4	9.44	13.00	0.5 cc. daily for 10 days.
Aug. 27	..	....	0.5 cc. daily for 10 days.
Sept. 29	17.05	5.13	No symptoms.
Oct. 27	12.14	6.96	
Nov. 12	10.71	5.00	
Dec. 3	12.73	....	Since Aug. 27, 1931 has taken some Ca lactate. Troublesome symptoms. 5 cc. 10% $CaCl_2$ i.v.
Mar. 2, 1932	....	....	5 cc. 10% $CaCl_2$ i.v.
Mar. 8	....	....	5 cc. 10% $CaCl_2$ i.v.
Mar. 12	8.96	....	
May 9	10.40	2.80	Poor appetite. Obliged to take bromide to sleep. Free from tetany.
May 16	10.18	2.49	1 cc. viosterol every 5 days.
June 9	12.16	2.12	1 cc. viosterol every 3 days.
June 15	12.89	....	0.6 cc. viosterol every 3 days. In evening vomiting and diarrhoea.
June 16	....	....	Some improvement.
June 17	....	....	Greatly improved, but poor appetite.
June 18	....	....	0.6 cc. viosterol.
June 20	....	....	Nervousness, insomnia, disturbed by dreams.
June 21	....	....	0.6 cc. viosterol.
June 22	12.66	2.80	Generally much improved.

With lapse of treatment her condition gradually reverted to that existing before any ergosterol administration, but again improved as the treatment was resumed.

Case 3. Miss F. N. Age, 35 years. In 1917 the right thyroid lobe was removed for relief from exophthalmic goiter. No details are available. Early in 1928 there began a recurrence of symptoms which became progressively more pronounced, including nervousness, weakness, dyspnoea, tachycardia and a metabolic rate of plus 120 per cent. On November 15, 1928, the left lobe was removed.

On January 6, 1929, the patient began to experience numbness and cramping of the hands and later, melancholia. The only treatment was Ca lactate. These symptoms became progressively more severe.

On December 5, 1930, calcium therapy was discontinued. Two weeks later 0.5 cc. of viosterol 10,000 X was injected. At this time the blood calcium concentration was 7.55 mgm., the inorganic phosphorus 5.44 mgm. On the following day the concentrations were respectively 5.70 mgm. and 7.64 mgm. Another injection of 0.8 cc. of viosterol was made. Tetanic symptoms had disappeared by

the next day. On December 23 the calcemia was 13.00 mgm. and inorganic phosphorus 6.90 mgm. The patient appeared to be normal in every respect. A third injection of 0.4 cc. of viosterol was given. On December 27 the calcemia was only 9.50 mgm. and phosphorus 10.25 mgm. The patient was then suffering from an attack of severe migraine and a pronounced carpal spasm developed on application of the tourniquet. It is believed that these symptoms, together with the blood analysis, represent toxicity from overdosage. Subsequent experience with this patient as well as others strongly supports this belief. These symptoms had disappeared three days later and the patient testified to marked improvement subjectively.

During the next six months treatment with viosterol was applied as symptoms required, usually 0.5 cc. every 10 days to two weeks. Occasionally it was necessary to supplement this with small doses of Ca lactate. Tetanic symptoms were never allowed to progress to a severe stage. The calcemia fluctuated between 7.00 mgm. and 13.40 mgm. There was less fluctuation of inorganic phosphorus. On July 7, 1931, severe carpal spasm occurred. The calcemia was found to have fallen to 5.06 mgm. The patient was unable to tolerate Ca lactate and objected to the intravenous injection. Consequently she was placed on a regime of 0.75 cc. of viosterol by mouth daily, supplemented by a teaspoonful of Ca gluconate twice daily. This combination was continued for seven days. On July 23 the calcemia was 14.40 mgm. and phosphorus 7.27 mgm. All tetanic symptoms had disappeared. No further treatment of any kind was necessary until August 20, when another similar period of treatment was begun, and still another period of treatment was necessary on September 27.

On October 30 was begun the administration by mouth of 0.15 cc. daily and this was continued until December 3. During this period the calcemia fluctuated between 11.23 mgm. and 9.38 mgm. But to our surprise on December 21 the concentration had increased to 15.11. And on December 26 there was recurrence of moderately severe tetany with a calcemia of 10.85.

We now began oral administration of 0.5 cc. of viosterol twice weekly until January 15, 1932, when Ca lactate was substituted with the hope that the viosterol might have produced alterations of sufficient permanency as to require only lactate to control the symptoms. However, there was again recurrence of symptoms, progressively more severe, until, on April 15, 1932, it was necessary to supplement the lactate with 0.3 cc. of viosterol every four days up to April 28, when all treatment was discontinued.

In spite of the fact that the patient was feeling well and was free from tetany, on May 24 she began taking 1 cc. of viosterol daily and continued this to June 10, when again treatment was discontinued. While she had enjoyed a month of freedom from any tetanic symptoms after a period of light treatment, this intensive period seemed to render her less resistant. At any rate, there was on June 19 a sudden onset of a severe headache that did not yield to aspirin treatment, and accompanied by a peculiar facial swelling which in this patient has occurred frequently and was always followed by an attack of tetany. She was now given 0.6 cc. of viosterol daily until the headache was abated, which was not until July 4. Thereafter she received 0.6 cc. every three days. On July 13 calcemia was 12.39 mgm. and the phosphorus concentration 3.07 mgm. At this time she was again free of any symptoms of tetany.

One of the striking things in this case is the initial lowering of blood Ca with symptomatic improvement. Another is the occurrence of mild symptoms with relatively high blood Ca. This patient was relatively refractory to a single dose of viosterol but improved markedly when given intensive treatment, with or without calcium. After cessation of the viosterol treatment on December 3, 1931, it required more than three weeks for tetany to develop. She was then, after another period of treatment, free of any symptoms; but nevertheless the blood Ca was not constantly elevated. After discontinuing viosterol on January 15, 1932, in spite of Ca medication, she experienced a return of all symptoms to a degree of severity comparable with that before any viosterol was given. This attack was abated by a further period of treatment.

Case 4. Mrs. M. G. Age, 38 years. A thyroidectomy was performed in January, 1927. Two days later she developed the typical carpal spasm of parathyroid tetany, accompanied by psychosis. She recovered promptly after intravenous administration of $CaCl_2$, followed by Ca lactate by mouth for a short period, the exact duration of which is not known. At various times during the following year she experienced mild tetanic symptoms but no treatment was applied. During 1929 she was obliged to take Ca lactate occasionally. In the summer of 1930, apparently without any preliminary disturbance, she underwent a severe generalized tetanic seizure. From that time on she was subject to rather frequent severe symptoms and was obliged to take increasingly larger amounts of Ca lactate, and occasionally an intravenous injection of $CaCl_2$. In spite of this, tetany of varying severity recurred almost daily.

On December 11, 1930, the blood Ca concentration was 8.81 mgm. and the phosphorus 5.75. A single dose of 0.5 cc. of viosterol by mouth on the 13th was ineffective. An intravenous injection of 1 cc. of viosterol a week later was evidently a toxic dose since severe pains appeared over the whole body, accompanied by marked weakness, diarrhoea and gastrointestinal pains. These are among the typical symptoms of overdosage in adult human beings as we have found repeatedly. However, the tetanic symptoms were entirely abated three days later. Calcemia was now 11.07 mgm. The toxic symptoms persisted in mild form for a week. Intravenous injections of 0.4 to 0.5 cc. of viosterol were given every two weeks but even this small dose was mildly toxic. But when supplemented with Ca lactate, it controlled tetanic symptoms. The viosterol was discontinued on January 24, at which time calcemia was 13.09 mgm. On March 13 the concentration was 10.80 mgm.; on April 16, 6.90 mgm. Then on May 1 the concentration increased to 10.97 mgm. and the phosphorus concentration was 10.25 mgm. She now voluntarily reduced the amount of lactate to about one-third the daily dose necessary during the preceding period. She had been receiving also 1 grain of desiccated thyroid daily.

On June 26 calcemia was 12.70 mgm., phosphorus 12.83 mgm. On August 18 the concentrations were respectively 11.10 mgm. and 9.40 mgm. In spite of these favorable concentrations, however, mild tetanic symptoms began to appear and she began taking 0.3 cc. of viosterol daily by mouth. Ca lactate administration was discontinued. After a total administration in this period of 5 cc. the calcemia was 15.30 mgm., the phosphorus concentration 7.92 mgm. All tetanic symptoms had disappeared.

On October 10 calcemia was still 13.70 mgm. but nevertheless definite and moderately severe tetanic symptoms began to appear. From this time until November 28 the patient received daily from 0.15 cc. to 0.3 cc. of viosterol by mouth. She now declared she was "feeling normal." All treatment was discontinued until January 2, 1932. In spite of generally good condition she resumed, for no definite reason, the consumption of small doses of Ca lactate daily, and continued this until March 12. Calcemia was now 8.32 and mild tetanic symptoms appeared. The oral administration of only 0.15 cc. of viosterol weekly was sufficient to alleviate these symptoms; however, on April 4 calcemia had fallen to 7.31 mgm. The phosphorus concentration was 3.86 mgm.

Case 5. Mrs. A. L. Age, 35 years. In February, 1927, a thyroidectomy was performed for toxic adenoma. An attack of tetany occurred the following day, which was relieved by Ca lactate administration which was continued several months. Finally all tetanic symptoms disappeared and no further treatment was necessary. About a year later mild tetany again occurred and from that time on fatigue, menses, an infection—such as a cold—or any other type of stress resulted in an exacerbation of these symptoms.

On March 5, 1931, Ca lactate administration was discontinued and 0.5 cc. of viosterol given intravenously. Calcemia at this time was 8.71 mgm., phosphorus 3.56 mgm. The symptoms did not completely disappear for a week. She was free from any recurrence until April 2, when mild tremors appeared with a calcemia of 13.00. Another injection of 0.5 cc. viosterol was given which was sufficient to render her symptom-free until June 4, when a third injection was necessary. Calcemia was now 10.55 mgm. Now, however, the reaction was quite different. During the following week there was severe and persistent headache, abdominal cramps and a vague generalized discomfort.

On June 11 calcemia was only 8.39 mgm., but the phosphorus concentration was 12.35 mgm. Tremors were severe enough that it was necessary to administer 5 cc. of 10 per cent $CaCl_2$ intravenously. Evidently this represents toxicity but it is not apparent why it should have occurred on this particular occasion.

However, similar reactions occurred so frequently thereafter that it was finally necessary to reduce the single dose to 0.3 cc. and supplement it with Ca lactate.

Finally, on Jan. 21, 1932, all treatment was discontinued and the patient remained in a normal state for a month. Then fine tremors, slight tingling and numbness and headaches began to occur. While these manifestations were of progressively increasing severity, it was not found necessary to resume treatment until March 14.

The most perplexing problem in this case was the proper grading of the dose. Apparently there was a rather narrow margin of safety between the threshold of effectiveness and the toxic dose. Numerous variations of the treatment were made but without any more favorable results.

This patient presents a somewhat less severe picture than the previous case and on the whole has responded more readily. While Ca lactate alone was not sufficient to alleviate the symptom complex, relatively mild viosterol dosage has maintained her free from any definite tetanic symptoms. But so far there is no indication of permanent cure, since symptoms recur after some time when viosterol is discontinued.

Case 6. Mrs. H. P. Age, 30 years. This case was first reported by Jacques (15). A thyroidectomy was performed on September 22, 1924, with evidence of severe tetany on the following day. For the subsequent history and details of treatment up to August 8, 1929, the reader is referred to this author's article (Case 1). In September of that year she entered a hospital for a condition described in the case history as "acute pelvic infection," but most of the following 6 weeks was devoted to an effort to control the severe tetanic attacks that were of frequent occurrence. Parathormone proved ineffective and Ca gluconate was not tolerated. Again the case history fails to give details. Brief mention was made to the effect that duodenal feeding was beneficial.

In April, 1931, the patient entered another hospital because of sinus infection. An operation to correct this condition was recommended, but was not done because of the severity of the tetanic seizures. She remained in this hospital 4 months. During 4 weeks she received daily intravenous injections of $CaCl_2$ or Ca gluconate. Parathormone in amounts up to 20 units 3 times a day was wholly ineffective. A lactose and milk diet resulted in severe gastro-intestinal disturbances with diarrhoea which resulted in as many as 51 bowel movements in one day. During 11 weeks a diet consisting only of milk and distilled water was given. During all this time she was never free from tetany for more than a few hours at a time. The highest blood Ca concentration was 7.20 mgm. A pelvic operation was recommended but was not done.

During June and July she was subjected to x-ray treatment for menorrhagia followed by cessation of menses. Early in September, 1931, this case came under our observation. The blood Ca concentration was 13.50 mgm., phosphorus 7.48 mgm. and yet severe and persistent tetany was present. The patient claimed that on one earlier occasion tetany had occurred with hypercalcemia of 14.00 mgm. From September 5 to 11, inclusive, she received 5 cc. of 250 D viosterol daily by mouth. There was pronounced improvement, although the calcemia was 10.63 mgm. and phosphorus 10.38 mgm. During the next four days she received 1 cc. of 10,000 X viosterol by mouth daily. Nevertheless, on the 14th occurred an attack of tetany so severe that it was necessary to resort to an intravenous injection of 5 cc. of $CaCl_2$. The calcemia was now 13.10 mgm. and phosphorus 10.13 mgm.

The daily dose of 1 cc. of viosterol orally was continued through September 28. The attacks of tetany were progressively less severe and less frequent until finally there was complete relief, although the blood concentrations of Ca and P were respectively 11.44 mgm. and 11.35 mgm. No tetanic manifestations were apparent October 10, when a period of treatment was instituted, with 0.5 cc. of viosterol daily through October 27, when mild symptoms of overdosage appeared. There were no tetany symptoms during this period in spite of a severe cold which would ordinarily have initiated tetany, according to both previous experience and subsequent observation.

On November 4, 1931, she entered the Research Hospital, remaining until January 16, 1932. During this time she received orally a total of 16.25 cc. of

viosterol, 10,000 X in doses ranging from 0.5 cc. to 0.75 cc. Both Ca and P concentrations remained fairly constant. Extreme variations of Ca were 8.10 mgm. and 12.50 mgm. On December 13 an interposition operation was done. This was followed by a severe bronchial infection which persisted for a week. During this period occurred the only attack of tetany while in the hospital. This was apparently correlated with a disturbance of acid-base balance. While the blood pH had not varied significantly from 7.4, on the day of this attack it rose to 7.66. The attack was relatively severe but of short duration. It might be presumed, therefore, that this was tetany of alkalosis.

For two weeks after leaving the hospital the patient remained in a convalescent home, but was able to come to the hospital for observation. She was now given 0.5 cc. of viosterol every five days, supplemented by Ca lactate and one intravenous injection of $CaCl_2$, when a severe attack occurred.

After returning to her home on February 2, 1932, there was gradual improvement, until she was able to resume all of her usual activities for the first time since 1924. While nervousness and muscular weakness sometimes appeared, she was, during most of the time up to July 7, subjected to only very mild tetanic symptoms. The exciting cause of the occasional severe attacks could not be determined. In general the concentration of the inorganic phosphorus in the blood was progressively reduced to 3.77 mgm. on July 7, but calcemia remained even more constant than during the hospital period.

One interesting feature of this case that is not readily apparent in the above description was the development and subsequent abatement of a psychosis. At the time she came under our observation, she presented a facies indicative of hysteria. By the time she left the hospital the change was very marked, although difficult to describe so that it could be fully appreciated except by direct observation. No other treatment accomplished this result even when the patient was kept free from tetany. Whether this is an incidental result, it is none the less definite and must be considered as an important factor in the use of this treatment.

It will be noted that this patient had become progressively refractory to treatment with parathormone and to calcium by mouth but is now able to dispense with calcium except as ingested in the food.

It is important also to note that at no time after viosterol treatment was begun was the blood calcium as high as at the time of the first observation on September 4, 1931, and yet there was almost constant evidence of tetany at that time. Furthermore, relief from tetanic seizures was sometimes accompanied by a decrease in blood calcium, sometimes by an increase, but often remaining unchanged.

Case 7. T. N. Male. Age, 59 years. Three operations were performed on this patient for relief of symptoms of exophthalmic goiter, the first in September, 1929, the second in May, 1930, and the third in April, 1931. One week after the last operation there occurred numbness and tingling in the hands and feet, carpal spasm and psychic disturbances. He was given an intravenous injection of $CaCl_2$, followed by 12 gm. of Ca lactate daily. In spite of this the symptoms became progressively worse until on June 2 he was admitted to the hospital. The blood Ca concentration was 5.22 mgm. and phosphorus 12.00 mgm. All calcium medication was discontinued. The patient at this time was almost constantly delirious.

On the following day an intravenous injection of 0.5 cc. of viosterol was given, followed by a second injection four days later. But on the following day the symptoms of tetany became so severe that another intravenous injection of $CaCl_2$ was given and daily administration of Ca lactate was resumed. There now began to be apparent progressive improvement. On June 22 daily oral administration of 0.5 cc. of viosterol was begun and continued to July 18.

On July 31 he was dismissed from the hospital. At this time calcemia was 13.33 mgm., phosphorus 5.48 mgm. From this time on until the last observation

on January 26, 1932, the only treatment was 4 gm. of Ca lactate three times daily. There was progressive decrease in the concentration of blood Ca to 6.93 mgm. The only symptom then present was a slight numbness of the hands. There was no recurrence of psychosis. He has gained weight and is active to a normal degree.

As suggested in connection with the first case, it is questionable whether the present condition may not represent spontaneously developed latent tetany. And it cannot be proved that such is not the case. Nevertheless, everyone of experience who observed him was of the opinion that he could not survive, so pitiable was his condition. Whatever may be the conclusion on that point, we feel justified in assuming that the viosterol treatment at least greatly assisted in the development of latent tetany and certainly alleviated to a great degree the patient's distress during the period necessary for the development of latent tetany.

Case 8. Mrs. E. C. Age, 57 years. In 1927 a thyroidectomy was performed for a toxic nodular goiter. A few days after the operation mild symptoms of tetany appeared. Four months later a generalized tetanic seizure occurred and the oral administration of Ca lactate was instituted. This treatment was continued but there was almost constant evidence of mild tetany. In 1930 a cataract developed in the right eye and was removed. Since then the left eye has become similarly affected.

The patient was admitted to the hospital on January 16, 1932. During a week of preliminary observation the inorganic phosphorus concentration in the blood was constantly higher than that of calcium. On January 25 Ca lactate was discontinued and 0.5 cc. of viosterol administered orally. This was repeated every five days. All tetanic symptoms were alleviated promptly. The blood Ca level was not significantly altered but the inorganic phosphorus was progressively decreased.

On February 11 she was discharged from the hospital. From that date to July 18 the history was very similar to that of the cases previously described. On this latter date the calcemia was 10.05 mgm. and phosphorus 3.94 mgm.

The history of this case during the interval from the operation to the time our observations were begun is very incomplete and unsatisfactory. While tetanic symptoms were constant and persistent, she evidently has never experienced as severe attacks as have most of the other patients. The occurrence of cataract is a feature to be noted. The steady reduction in inorganic phosphorus is worthy of consideration, although this phenomenon is apparent to some extent in the other cases. The calcium concentration was not persistently at a low level for any length of time after treatment was begun and has since been maintained at a low normal level. She has taken no calcium lactate since April 29. It is believed that the treatment as now applied will maintain her free from tetany indefinitely.

Case 9. Mrs. G. Age, 60 years. In 1910 a thyroidectomy for exophthalmic goiter was performed. In February and November, 1929, two similar operations were done. About six months after the last operation she began to experience numbness, tingling and cramping of the hands. These symptoms were never severe but Trousseau's sign could be elicited most of the time. Calcium medication was very rarely resorted to.

On April 6, 1931, the calcemia was 8.53 mgm., phosphorus 12.10 mgm. An intravenous injection of 0.5 cc. of viosterol was made and on April 26 another of 1 cc. Within a few days all of these symptoms had completely disappeared. The calcemia has never risen above 11.07 mgm. On June 5 the calcemia was 9.44 mgm., phosphorus 3.62 mgm.

This case was characterized by very mild but persistent tetanic symptoms that were completely abated by the two doses of viosterol.

Case 10. Mrs. D. Age, 23 years. A thyroidectomy was performed in the fall of 1930. Soon afterward she developed stiffness and tetanic cramps in the hands, so that she was unable to use them. She was taking calcium lactate in doses up to ¼ pound daily. In addition injections of parathormone were made, but the symptoms were never completely alleviated.

January 29, 1931. Ca 7.55, P 8.11. Spontaneous carpal spasm and twitching of the facial muscles. All calcium medication discontinued. 0.5 cc. 10,000 X viosterol i. v.

January 30, 1931. Severe generalized contractions, bordering on convulsion. Calcium lactate by mouth.

January 31, 1931. Ca 6.63, P 8.80, 0.5 viosterol; Ca 8.39, 0.5 cc. viosterol. Has pains in feet and twitching of the face.

February 6, 1931. Ca 7.19, 0.5 cc. viosterol. No subjective symptoms. Better than at any time previously.

This case was lost at this point and the subsequent history is not known. The point of significance is that subjective discomfort was abated without any significant elevation of blood calcium concentration.

Other case histories are not complete enough to justify inclusion at the present time.

DISCUSSION

There are certain obvious criticisms which may be made of this report. First, records are much less complete than would have been desirable. But at that we feel that we have covered the most essential points. Second, some of the patients were never hospitalized in connection with this investigation, and none of them for very long periods. Consequently, not all factors were controlled at all times and furthermore we were forced to rely on their testimony as to symptoms, activity and treatment at home. But it was found very early that all of these patient came to fear and dread tetanic attacks. Consequently, they could be impressed with the necessity of adhering strictly to instructions as to home regimen. They were all of a high order of intelligence and readily cooperated, once they became impressed with the possibilities of benefit. Each patient was instructed to keep a diary, entering accounts of symptoms and treatment.

Another criticism lies in the fact that the diet was not standardized under home conditions.

While three patients have had no treatment for over a year, we are still unwilling to consider them cured. It will be noted that all of these patients have experienced long periods—as much as two years—of comparative freedom from tetany, followed by spontaneous development of severe and persistent symptoms. One of the three had, however, suffered mild but persistent symptoms over many years. These patients will be observed and future developments reported.

Of the six cases still under observation all the subjects are free from severe tetany while on comparatively heavy medication with viosterol, but so far they have all shown recurrences after varying periods of time when viosterol administration was discontinued.

An examination of the histories makes it apparent that the extent of treatment necessary has varied somewhat from time to time. This probably depends on many factors, too complicated to permit of analysis.

It will be further noted that the patients that have suffered most severely had all become refractory to calcium medication and to parathyroid extract in the form of parathormone. So far, there is no evidence that any of them have become similarly refractory to viosterol. Only continued observation for a longer period will settle that point. Judging from animal experiments made in this laboratory, it seems unlikely that such tolerance will develop.

As already mentioned, the intravenous route of administration seems to be more effective. This is readily understood when it is realized that as high as 40 per cent of orally administered irradiated ergosterol has been recovered unchanged from the feces. Then, too, some of it is likely to be changed to coprosterol and so inactivated. This makes it apparent then that there may be considerable waste of material by the oral route.

So far we have found no satisfactory criteria for prediction of the minimum effective dosage except by trial. Our general rule has been to give heavy medication and by gradually reducing the amount administered over a given period of time to arrive at this point. On this basis the employment of this treatment becomes a matter of careful and patient trial in each case over a long period.

In spite of the close correlation between the blood Ca level and the onset of tetany in experimental parathyroid deficiency, it is apparent from these cases that there is no such close correlation in the long standing cases. Clinical tetany may occur with hypercalcemia and the alleviation of tetany may accompany a lowering of the Ca content even to a low normal.

One of the theories of functioning of irradiated ergosterol holds that it stimulates the parathyroids. Results obtained in this laboratory on animals, to be published elsewhere, demonstrate conclusively that at least a part of the effect is produced through some other mechanism. In spite of what must have been a pronounced parathyroid deficiency in some cases, it was possible to produce practically as free a response to viosterol as occurs in normal subjects. Of course, it may still be argued that parathyroid remnants are stimulated.

In some cases the inorganic phosphorus content of the plasma was very high when the patients first were placed on viosterol. In general there was a tendency toward a lower level as treatment progressed. This tendency seems to be an important feature of the general improvement and should be carefully investigated when undertaking this treatment.

Clinical tetany, which is immediately due to parathyroid deficiency, is a disturbance of metabolism of both Ca and P and possibly other related factors. Tentatively, we suggest that the rôle of viosterol in producing the beneficial results obtained is not primarily that of raising the Ca content or of lowering the P content, but is one of stabilization of Ca-P metabolism and whatever other factors may be involved, regardless of the direction. The exact mechanism remains to be determined. Such a concept will, we believe, explain our results more satisfactorily than any other.

SUMMARY AND CONCLUSIONS

1. Ten patients with clinical parathyroid tetany of varying degrees of severity and duration have been treated with varying amounts of irradiated ergosterol in the form of viosterol 10,000 X.

2. All patients so treated have been benefited not only in control of tetanic symptoms but in a general stabilization of the subjective condition in a manner not possible by treatment with parathyroid extract or with Ca salts, alone or in combination.

3. With careful observation this potent preparation of viosterol may be administered safely to human subjects in amounts up to 1 cc. daily for several days without danger of toxic conditions developing.

We extend to Dr. C. S. Williamson our appreciation of his cooperation in providing hospital facilities, and to Mrs. M. E. Millikan for technical assistance, and to Mead Johnson and Company for generous supplies of viosterol.

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DOES THE ANTERIOR-HYPOPHYSARY SUBSTANCE PREPARED FROM PREGNANCY URINE RAISE THE BLOOD-SUGAR LEVEL?

E. DINGEMANSE AND S. KOBER

From the Pharmaco-Therapeutic Laboratory of the University of Amsterdam. Director, Prof. Dr. E. Laqueur

AMSTERDAM

In his paper on the "Effect of anterior pituitary hormone upon blood sugar,"* Eidelsberg states that he obtained a marked rise in fasting rabbits after injection of 100 units of "Hebin." This substance represents the sexual hormone of the anterior pituitary, prepared from pregnancy urine by a modification not further specified, of the method of Aschheim and Zondek. According to the author a rise of at least 40 mgm. per 100 cc. should occur with a preparation of unchallengeable activity. The highest rise he observed was 220 mgm. but the average was only 100 to 175 mgm. per 100 cc. The highest level is reached within ½-2 hours, and in the average cases between 1 and 1½ hours. With lower doses a similar, but less marked effect was obtained. The injections were given into one of the ear veins, blood samples were drawn out of a vein of the thighs Blood sugar was estimated by the Folin-Wu method.

In three series of experiments a reproduction of the results of Eidelsberg was attempted. One difficulty that arose, however, was the lack of a reference to Eidelsberg's method of standardization according to which the units of the anterior hypophysary substance were determined. Our own definition is that of rat units (according to the procedure of S. Janssen). At the most, 10 of these units correspond to one corpus luteum unit as determined on the ovary of the infantile mouse. On one point the procedure described by Eidelsberg was knowingly departed from in these experiments, in that blood samples were taken from the ear and the blood sugar estimated by the method of Hagedorn-Jensen.

All the results in the tables are calculated as an average of two estimations. In these experiments two preparations of the anterior hypophysary substance made from pregnancy urine were used. One of these, D Y, was comparatively highly purified, the rat unit being contained in 0.0133 mgm. (Our purest preparations have at present a purity of 0.001 mgm.) The other was a crude extract H V 48, of which the unit weighed 0.417 mgm. per rat unit. The latter preparation was also used after destruction of the hormone by boiling. The quantity injected was in every case dissolved in 1 cc. water. In the following three tables the results are presented as collected on three different days of injection.

*Eidelsberg, J.: Proc. Soc. Exper. Biol. & Med. **29**: 959. 1932.

TABLE 1

Rabbit		Injected With			Blood Sugar Per Thousand			Maximal Deviation From Normal
No.	Weight	Preparation	Number of Units	mgm.	Normal	¾ Hr.	1½ Hr.	
87.....	2200	D Y	100	1.33	1.56	1.10	1.10	—0.46
103.....	1700	D Y	100	1.33	1.25	1.40	1.22	—0.03
Average...	1950	D Y	100	1.33	1.40	1.25	1.16	—0.24
146.....	1850	D Y	400	5.32	1.40	1.32	1.24	—0.16
40.....	1850	D Y	400	5.32	1.45	1.04	1.10	—0.35
Average...	1850	D Y	400	5.32	1.42	1.18	1.16	—0.26

TABLE 2

Rabbit		Injected With			Blood Sugar Per Thousand			Maximal Deviation From Normal
No.	Weight	Preparation	Number of Units	mgm.	Normal	¾ Hr.	1½ Hr.	
111.....	1900	HV 48	400	166	1.32	1.51	1.77	+0.45
117.....	2200	HV 48	400	166	1.10	1.30	1.48	+0.38
Average...	2050	HV 48	400	166	1.21	1.40	1.62	+0.41
140.....	1900	HV 48	100	42	1.24	1.17	1.53	+0.29
31.....	2000	HV 48	100	42	1.16	1.07	1.41	+0.25
Average...	1850	HV 48	100	42	1.20	1.12	1.47	+0.27

TABLE 3

Rabbit		Injected With			Blood Sugar Per Thousand				Maximal Deviation From Normal	Remarks
No.	Weight	Preparation	No. of Units	mgm.	Norm.	¾ Hr.	1½ Hr.	2 Hr.		
16.....	2400	HV 48	1000	417	1.46	1.93	2.04	1.59	+0.58	Died 8–23 h.
128.....	1800	HV 48	1000	417	(1.20)	....	....	....	.....	Died immediatly after injection.
Average...	2100	HV 48	1000	417	....	....	....	....	.....	
78.....	2200	HV 48	0	208	1.35	1.03	1.73	1.01	+0.38	
96.....	2100	Destroyed	0	208	1.33	1.29	1.64	1.68	+0.35	Died after 24 h.
Average...	2150	Destroyed	0	208	1.34	1.16	1.68	1.34	+0.34	
116.....	2400	D Y	1000	13.3	1.41	1.33	1.12	1.06	—0.35	
56.....	1900	D Y	1000	13.3	1.23	1.18	No Blood	No Blood	(—0.05)	
Average...	2150	D Y	1000	13.3	1.32	1.35	....	....	.....	

From these tables the following conclusions are drawn. In Table 1 it is shown that injection of 100-400 rat units of a purified preparation causes an average fall of blood sugar of 0.24-0.26 per thousand. The lowering was the largest in rabbit 87, attaining as much as 0.46 per thousand. Injection of 1000 units of the same preparation caused a fall of blood sugar of rabbit 116 by 0.35 per thousand.

In Table 2 a rise of blood sugar after injection of 100-400 units of a crude preparation HV 48 is seen. This ranges from 0.27 to 0.41 per thousand. The maximum effect is reached in rabbit 111, after injection of 400 units, amounting to a rise of 0.45 per thousand.

In Table 3 an attempt is shown to increase the dose of the crude preparation to 1000 units. One of the animals thus treated died immediately after the injection (No. 128), while the other survived and reached

a maximal height of blood sugar level after 1½ hours (0.58 per thousand higher than normal).

Considering the toxicity of the preparation in such high concentrations, in another group (Nos. 78 and 96) half of the dose was injected after destruction of the sexual hormone by heat. An average rise of blood sugar level by 0.34 per thousand was observed and the maximal rise was 0.38 per thousand. These results correspond fairly well with those of Table 2.

SUMMARY

Injection of large doses of a purified anterior hypophyseal preparation made from pregnancy urine, up to 1000 rat oestrus units, does not raise the blood sugar level. At variance, there appears rather constant lowering, which does not seem to depend on the dose applied and which averages 0.30 per thousand.

By injection of a crude preparation, a rise of the blood sugar level is found, although less in extent than stated by Eidelsberg, but this seems, in accordance with him, to depend to a certain extent upon the dose applied. The highest rise observed was 0.58 per thousand. A similar effect was obtained by injecting the crude preparation, in which the sexual hormone was destroyed by heat. No apparent difference was seen as compared with the active preparation.

Since neither the comparatively pure preparation nor crude preparations whose activity has been destroyed have an effect of raising the blood sugar level, we are led to conclude that the effects observed by Eidelsberg are independent of the anterior hypophysary sex hormone, extracted from pregnancy urine, and are due to substances other than this hormone.

THE RELATION OF THE THYROID TO THE HYPOPHYSIS AND OVARY*

W. M. VAN HORN
From the Zoology Department, University of Wisconsin
MADISON

INTRODUCTION

That the secretions of the thyroid gland play an important part in the physiology of reproduction seems fairly well established. The fact that the thyroid gland becomes enlarged at puberty, during menses, and during pregnancy was observed by earlier investigators, and furnishes, perhaps, the first record indicating this relationship. Gudernatsch (1915) found that thyroid substance, whether administered to male or female rats had a tendency to prevent pregnancy, and when pregnancy occurred, to produce abortion. Kunde, Carlson, and Proud (1929) fed thyroid substance to rabbits, and found that there was the occurrence of oestrus, ovulation, fertilization, migration and implantation of ova, but during the latter two-thirds of the gestation period the embryos were resorbed. Similarly, Weichert (1930) found that feeding one-fourth to one-half of a gram of desiccated thyroid daily to pregnant rats caused resorption of young in some animals, abortion in others, and in some cases a prolonged period of gestation with the ultimate delivery of dead young. He also found that the administration of thyroid to non-pregnant rats in comparable doses produced a dioestrous condition after two oestrous cycles, which was maintained as long as the thyroid treatment continued. He suggested that this dioestrus was due to the persistence of the corpus luteum brought about in some way by the condition of the anterior lobe of the hypophysis in hyperthyroidism. Moreover, it was suggested that the delayed parturition may be due to a lack of the oestrus producing hormone following increased metabolism. Lee (1925), in his studies on the oestrous cycle in the rat, found that following thyroidectomy there was, on the average, a one-day lengthening of the cycle. His results also indicate that pre-pubertal thyroidectomy did not materially change the length of time at which sexual maturity was reached. He offers two alternate explanations: (a) Normally the thyroid exercises a stimulating influence upon the ovary, and the removal of this stimulus causes a lengthening of the cycle; (b) Ovarian activity varies with general body activity, and thyroidectomy affects the oestrous cycle through its effect on metabolic processes. Quite contrary to the former explanation Reiss and Pereny (1928) reported that the thyroid autocoid was antagonistic to the ovarian hormone (theelin) in both the

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normal and castrate animal, although a quantitative relationship is not indicated. There is also the possibility that the thyroid has an influence on the normal functioning of the hypophysis. Various workers have reported that both the hyperthyroid and hypothyroid conditions in the albino rat have their effect on this gland. Thus Evans and Simpson (1930) observed that the gonad stimulating properties of the anterior pituitaries from hyperthyroid rats were increased, while the glands from hypothyroid rats were less effective than normal. They report a qualitative relationship only. Smith and Engle (1930) found that 200 days after thyroidectomy there was no constant difference in the gonad stimulating effect. They point out that such a result is to be expected, since thyroid ablation does not cause any severe upset to the rat reproductive system.

Uhlenhuth and Schwartzbach (1927) observed that metamorphosis in certain salamander larvae may be effected prematurely by the administration of anterior pituitary substances; this metamorphosis was not a result of the direct action of these substances, but was the result of the activity of the thyroid gland which had been stimulated to great activity due to the presence of the anterior pituitary material. Their studies showed further that under the influence of anterior pituitary substances, the colloid is released from the thyroid acini. This latter phenomenon has been observed by Loeb and his co-workers (1932) in the thyroid acini of immature guinea pigs. In these investigations no attempt was made to determine which hormone of the anterior lobe was responsible for this activity, nor is any mention made of the relative potency of the preparations used, except in some cases as to the size of the portions administered.

Engle (1929) and Evans and Simpson (1929) found that the gonad stimulating power of the hypophysis increased after castration. Meyer, Leonard, Hisaw and Martin (1930) have shown that this power of the hypophysis is inhibited under the influence of the oestrus producing hormone. In view of these data, coupled with the report that the thyroid is antagonistic to follicular activity, the question arises as to whether or not the thyroid affects the hypophysis by neutralizing the effects of theelin. If this is the case, to what extent can this relationship be placed on a quantitative basis? If the thyroid is able to inhibit the action of theelin, will it also inhibit the action of the corpus luteum hormone, namely corporin? That a thyroid-pituitary relationship exists provokes speculation concerning the effect of thyroid secretions on the pituitary. In the presence of an abnormal amount of thyroid substance will the secretions of the pituitary be able to fulfill their usual function? The studies presented in this paper represent an attempt to obtain information concerning these inter-glandular relationships.

EXPERIMENTAL PROCEDURE

Both hyperthyroid and hypothyroid animals were used in the course of this work. Concerning the methods by which the animals were placed

in either a hyperthyroid or a hypothyroid state, the procedure was not dissimilar to that followed by other workers. When a hypothyroid state was desired, thyroidectomy was resorted to.

A hyperthyroid condition was produced in the rats by a method similar to that described by Weichert (1930). The animals were fed from 625 to 1000 mgm. per kgm. body weight of desiccated thyroid powder per day. The thyroid powder was weighed and mixed with enough water so that 1 cc. of the resulting suspension contained a daily dose. This mixture was administered orally by means of a bulb pipette, which was calibrated for 1 cc. For the first few administrations, until the animals became accustomed to eating from a pipette, a small amount of sugar was added. For the most part, fresh mixtures were made each day, since it was found that the animals took the material better when it was fresh.

The criteria by which the animals were judged to be in a hyperthyroid state were, first, a distinct and progressive loss in body weight, and second, in those cases where normal animals were used, the maintenance of a dioestrous condition for a period corresponding to at least four normal oestrous cycles. In all cases the hyperthyroid animals exhibited a roughened coat, a loss of fine hair, and manifested extreme nervousness and pugnacity.

I. *Influence of Thyroid Feeding on the Activity of Theelin.*

Twenty-four sexually mature female rats were ovariectomized and after eight days were brought into artificial oeostrus by the injection of theelin.* The minimal amount of theelin necessary to produce experimental oestrus, when injected at three equal and consecutive doses at eight-hour intervals, was taken as one rat unit. After it was found that the animals would respond to one rat unit of theelin, they were fed 625 mgm. per kgm. of body weight per day of desiccated thyroid powder, for a period of five weeks. At this time they were given, in addition to the thyroid administration, one rat unit of theelin, and vaginal smears were taken for a suitable length of time to determine if an oestrous condition was induced. Under these conditions oestrus was never observed. After an elapse of eight days, two rat units of theelin were injected. Again, an oestrous condition was not produced in any case. After another eight days, the dosage of theelin was increased to three rat units, which produced a definite oestrus reaction in 20 of the 24 animals, as indicated by the presence of either nucleated or cornified cells in the vaginal smears. The thyroid feeding was discontinued at this time, and the animals were allowed to recover their normal weight, after which a subsequent treatment of only one rat unit of theelin succeeded in producing oestrus in 14 cases.

These data indicate that approximately three times as much theelin is required to produce an oestrous condition in a hyperthyroid castrate rat, as in an ordinary castrate. This fact is of fundamental importance since

*Obtained through Dr. Hisaw from Parke, Davis & Co.

it shows a possible quantitative relationship between the secretions of the thyroid and the follicular hormone. According to these results, when 625 mgm. per kgm. of body weight per day of the sample of desiccated thyroid used in this experiment is administered, it requires three times the amount of theelin to produce artificial oestrus. Hence it is reasonable to assume that the extent of the effects due to theelin in the normal body may be influenced by the thyroid gland. Although the inhibition of the follicular hormone due to thyroid secretion is not understood, previous experiments have shown that both thyroid and ovarian activity depend on the hypophysis. From this fact it seems quite possible that the hypophysis may be concerned in the ovarian-thyroid relationship. Meyer, et al. (1930), and others have shown that the gonad stimulating properties of hypophyses of animals treated with theelin is decreased. Moreover, it is known that the gonad-stimulating power of the hypophysis is increased with the elimination of ovarian activity. Since it seems quite probable that thyroid feeding, in some way inhibits the action of theelin, the question arises as to what effect an abundance or an absence of thyroid substance will have on the gonad-stimulating properties of the hypophyses. Would a hyperthyroid condition increase the effect of the hypophysis on the gonads, and similarly, would a hypothyroid condition decrease these effects?

II. (a) *The Relation of the Thyroid to the Hypophysis as Indicated by the Implantation of Anterior Pituitaries from Hyperthyroid Rats.*

It has been observed that a hyperthyroid condition in a rat may cause a disturbance in the normal oestrous cycle. This fact suggests the possibility that such a condition would lower the amount of theelin present in the animal, and since theelin inhibits anterior lobe action, the further possibility that the gonad-stimulating power of the anterior lobe might be increased.

Twenty-four sexually mature female albino rats, of uniform age, weighing from 160 to 200 grams, and with normal oestrous cycles, were fed on desiccated thyroid powder on a dosage of 900 mgm. per kgm. of body weight per day. When the animals had remained in a dioestrous condition for a length of time corresponding to at least four normal cycles, their anterior pituitaries were implanted into 20-day-old female litter mate rats. In some cases two glands were implanted into the recipients, and in others three glands were used. The recipients were arranged in such a way that experimental and control pituitaries were implanted into different members of the same litter. The control pituitaries were taken from normal female rats, corresponding in age and weight to the experimental animals. The data and results of this experiment are recorded in Table I. For convenience in comparison the litters used in testing these pituitaries were divided into four groups, each group representing one litter. The greatest increase in gonad-stimulating power is seen in Group II, whereas the lowest is in Group III. The data for this experiment indicate that in

some way the thyroid hormone, when present in abnormal amounts, is capable of increasing the ability of the hypohysis to stimulate growth of the immature ovary.

TABLE I

THE EFFECT OF FEEDING THYROID ON THE HYPOPHYSES OF NORMAL FEMALE RATS

Donor Rats	Body Weight	Type	Recipient	Weight of Recipient Ovaries	Average	% Increase
			GROUP I			
LN	171	Hyp.	LN	.0134		
L3N	146	Hyp.				
L2N	156	Hyp.	L3N	.0134	.0134	
R3N	150	Hyp.				
RN	175	Con.	L2N	.0096	.0096	39
R2N	138	Con.				
			GROUP II			
RN	189	Hyp.	L2N	.0187	.0240	63
L2N	133	Hyp.				
LW	190	Hyp.	L3N	.0293		
R3N	140	Hyp.				
RW	149	Cor.	RH	.0152	.0147	
NM	162	Con.				
R2N	203	Con.	R2H	.0143		
RH	134	Con.				
			GROUP III			
RN	135	Hyp.				
R2N	170	Hyp.	RN	.0126		
R3N	140	Hyp.				
LN	145	Hyp.				
L2N	160	Hyp.	R2N	.0130	.0129	15
R3H	137	Hyp.				
RNB	168	Hyp.				
R2NB	151	Hyp.	LN	.0130		
LNB	140	Hyp.				
L2N	150	Con.				
L2NRH	160	Con.	R3N	.0112		
L2H	144	Con.				
			GROUP IV			
L2H	155	Hyp.				
R2H	150	Hyp.	RHN	.0180	.0180	
L2NB	140	Hyp.				
L2N	138	Hyp.				
L3N	155	Hyp.	RH2N	.0190		42
L3H	162	Hyp.				
NM	159	Con.			.0130	
LNR2N	152	Con.	RHLN	.0130		
LNRN	140	Con.				

"Hyp." indicates animals in a hyperthyroid condition. "Con." indicates control animals. In groups I and II two pituitary implants were made into each recipient, and in groups III and IV three implants were made.

The question arises as to the nature of the mechanism that causes this effect. Does the thyroid act directly upon the hypophysis to stimulate its secreting activities, or does it act indirectly through the medium of some other agency? It has just been shown that the action of theelin is inhibited by thyroid feeding. Since it is known that theelin is capable of decreasing the gonad-stimulating property of the pituitary, it seems probable that the

thyroid by eliminating theelin, might indirectly cause the increase in pituitary potency.

To test this possibility, 12 sexually mature rats, of uniform age and weight, were ovariectomized, and fed 900 mgm. of desiccated thyroid powder per kgm. of body weight per day for six weeks. The hypophyses of these animals, when implanted into sexually immature female rats, showed no significant increase in gonad-stimulating power over the natural increase of castrate female controls. (Table II.) Theelin as a modifying

TABLE II

EFFECT OF FEEDING THYROID ON THE HYPOPHYSES OF CASTRATE FEMALE RATS

Donor Rats	Body Weight, Grams	Type	Recipient	Weight of Recipient Ovaries, Grams	Average	% Increase
			GROUP I			
LH	162	Hyp.	RN	.0195	.0160	
L3N	160	Hyp.				
RH	185	Hyp.	R2N	.0126		No significant change
R3N	151	Hyp.				
LN	180	Con.				
R2N	192	Con.	R3N	.0159	.0159	
			GROUP II			
LN	173	Hyp.	RH	.0542	.0540	
L2N	148	Hyp.				
LNH	205	Hyp.				
R2N	198	Hyp.	R2H	.0538		No significant change
RN	215	Con.				
R2N	201	Con.	R3H	.0577	.0577	
			GROUP III			
L2H	181	Hyp.	RN	.0255	.0273	
RN	192	Hyp.				
L2NH	177	Hyp.	R2N	.0291		No significant change
R2N	199	Hyp.				
RN	173	Hyp.	R3N	.0298	.0285	
R2N	188	Hyp.				
L3N	200	Con.				
RH	182	Con.	LN	.0273		

"Hyp." and "Con." indicate hyperthyroid animals and control animals, respectively. In all cases two donor pituitaries were implanted into each recipient.

influence is eliminated by castration, and it seems probable that if the thyroid is capable of affecting the hypophysis directly, there would be an increase in the gonad-stimulating power of the anterior pituitaries of these animals. However, the evidence from this experiment does not support this idea, but further indicates that theelin is the medium through which the thyroid is able to produce this effect.

Since a hyperthyroid condition seems to effect an inhibition of the action of theelin, it seems quite probable that a hypothyroid condition may permit an accumulation of theelin and thus decrease the gonad-stimulating power of the hypophysis. Accordingly 12 sexually mature female rats, having normal cycles were thyroidectomized; two, however, were found, at the time of necropsy, to have regenerated a small amount of thyroid tissue.

and so were not included in the data. Vaginal smears of these animals were continued from the time of the operation until their pituitaries were implanted, a period of six weeks. These smear records indicate an irregularity in the oestrous cycles which was not found prior to thyroidectomy. In two cases the cycle was noticeably shortened and in several there was a prolonged appearance of cornified cells. Hypophyseal implants from these animals, two glands to each recipient, showed no difference in gonad-stimulating properties beyond normal variation of controls. This is in agreement with the findings of Smith and Engle (1930) and indicates that since the oestrous cycles are not inhibited, there is enough theelin present to keep the gonad stimulating power of the hypophysis within normal range.

(b) *The Relation of the Thyroid to the Hypophysis Indicated by the Injection of Certain Anterior Lobe Extracts.*

A total of 20 female rats, with normal oestrous cycles, and ranging in weight from 150 to 200 grams, were fed desiccated thyroid powder, 900 mgm. per kgm. of body weight per day, until they had been in a dioestrous condition for a period corresponding to at least four normal oestrous cycles. They were then divided into six groups, and injected with varying doses of anterior pituitary extract. This extract was prepared after the method of Fevold, et al. (1931), which contained more of the follicular stimulating substance than the luteinizing, though the latter was present in quite large quantities. The animals received two injections per day for five days; although the dosage was different for each group the liquid volume administered was the same. Each animal in Group I received extract equivalent to 0.25 gram of the dried powder during the five-day treatment. Group II received 0.50 gram equivalent per animal, Group III 0.75 gram equivalent per animal, Group IV 1.0 gram equivalent, and Group V was left uninjected as controls.

Twelve hours after the last injection, the animals were killed and their ovaries weighed and sectioned for microscopic examination. Table III shows graphically the results of this experiment. It can be seen that there was a progressive increase in the weight of the ovaries as the dosage was increased. It is important to note that the stimulation furnished by a total of 0.25 gram equivalent of the dry powder was insufficient to produce an oestrous condition in the hyperthyroid rats (0.25 gram produced oestrus in control animals), but a larger dose produced oestrus in every case. Although a dioestrous condition existed for an extended period due to the feeding of thyroid tissue, in those animals where oestrus occurred, it seems that when the ovaries were stimulated by the pituitary extract, more theelin was secreted than could be inhibited, and in consequence the threshold value for oestrus was reached.

To determine the difference, if any, in the reaction of a hyperthyroid animal to anterior pituitary extracts as compared to a normal animal, eight hyperthyroid and nine normal female rats were injected with one gram

equivalent of dried sheep pituitary powder. Five days after the last injection the animals were killed and their ovaries weighed. It was found that the ovaries of the hyperthyroid rats were slightly heavier, but not significantly so. All ovaries had increased in weight approximately 40 per cent. The pituitary glands of all these animals were implanted into sexually immature female rats to determine if the high gonad-stimulating content of the pituitaries of hyperthyroid rats was maintained in the face of the anterior pituitary extract treatment. When the ovaries of the immature rats were weighed it was found that approximately the same amount of stimulation was produced by the pituitaries of the hyperthyroid rats as was produced by the controls.

A microscopic examination of these ovaries showed the presence of a great many corpora lutea, and very few follicles. In addition to the effects observed in the ovaries, there were also quite interesting changes in the thyroid gland. Loeb (1932) reported that the administration of anterior pituitary extracts caused a release of colloid from the thyroid acini of immature guinea pigs.

TABLE III

EFFECTS OF THE ADMINISTRATION OF ANTERIOR PITUITARY EXTRACTS ON OVARIES OF HYPERTHYROID FEMALE RATS

Rat	Dosage Gram Equivalent	Weight, Grams	Weight of Ovary	Average Weight of Ovaries Grams	Remarks
RN	0.25	171	0.0676		No oestrus
R2N	0.25	150	0.0445	0.0592	No oestrus
R3N	0.25	146	0.0656		No oestrus
LN	0.50	146	0.0732		Oestrus
L2N	0.50	133	0.0957	0.0917	Oestrus
L3N	0.50	185	0.1062		Oestrus
R2H	0.75	149	0.0963		Oestrus
R3H	0.75	190	0.1100	0.1166	Oestrus
RNH	0.75	158	0.1434		Oestrus
LH	1.00	166	0.2338		Oestrus
LNH	1.00	160	0.1715	0.2004	Oestrus
R2NH	1.00	140	0.1959		Oestrus
RH	....	190	0.0577		No oestrus
L3H	....	175	0.0906	0.0696	No oestrus
L2H	....	160	0.5060		No oestrus

It is well known that the thyroid acini of hyperthyroid animals are gorged with colloid substance to the extent that the cells lining them appear squamous. It is interesting to note that in the experiment just described there was no appreciable release of colloid from the thyroid acini, due probably to the fact that a hyperthyroid condition did exist. Injections of the same pituitary extract in equivalent dosages into normal animals did effect a colloid release, with a distinct heightening of the epithelium lining the acini. Apparently then, under the conditions of experimentally produced hyperthyroidism, the colloid material normally secreted by the thyroid gland is stored in the acini, and stimulation applied by the administration of anterior pituitary extracts is unable to effect a release.

From these experiments it can been seen that the gonad stimulating extracts of sheep anterior pituitary, when injected into a hyperthyroid

animal, cause a distinct increase in ovarian growth. This particular preparation, in other words, seemed capable of performing its normal function in spite of the fact that there was a large abundance of thyroid substance present. Although the data are not extensive, they indicate that a hyperthyroid condition does not produce any marked modification of the gonad-stimulating activities of the anterior lobe of the hypophysis.

DISCUSSION

The data presented in this paper strongly suggests the possibility that the thyroid exerts an influence on follicular activity, and also establishes a quantitative relationship between the thyroid secretion and that of the follicle. This work is in agreement with that of Reiss and Pereny (1928), who observed that the thyroid secretion was antagonistic to follicular activity, and the work of Weichert (1930), who found that rats fed on thyroid went into a prolonged dioestrus. The exact causes of these ovarian effects are not fully understood, but from the work presented here, it seems probable that the increased metabolism incident to a hyperthyroid condition is instrumental in the elimination of theelin, thus keeping the amount of theelin in the body below the threshold value required for the production of an oestrous condition. This idea, previously suggested by both Weichert (1930) and Van Horn (1931) receives considerable support from the data presented here for the effects of theelin on hyperthyroid castrate rats. Though the results may vary with the different samples of thyroid powder used, it is generally necessary to inject three times the usual amount of theelin to produce artificial oestrus.

It has also been found that the hyperthyroid condition produced by feeding thyroid substance to normal female rats is associated with an increase in the gonad-stimulating power of the hypophysis. This fact is supported by the work of Evans and Simpson (1930), who, employing a technique different from that used in this work, found that the gonad-stimulating power of hypophyses taken from hyperthyroid rats was increased, though a quantitative relationship is not indicated. It seems plausible to explain this on the basis of the effects of thyroid substance on theelin, for if the theelin normally secreted by the ovary was eliminated due to the thyroid, then the inhibiting effect of theelin on the hypophysis would be removed, resulting in an increase in the potency of the hypophysis. It is known (Engle, 1929, and Evans and Simpson, 1929) that castration increases the gonad-stimulating power of the hypophyses of rats. Further, Meyer, et al. (1930), showed that the injection of theelin decreases the gonad-stimulating power of the hypophysis. The fact that normal rats, fed on thyroid, go into a dioestrous condition indicates a value for theelin below the threshold required to produce oestrus. This condition approaches, then, that which exists in a castrate female rat, hence it would be expected that the potency of the hypophysis would be increased.

Additional evidence that theelin is the agent through which the thyroid is able to affect the hypophysis is presented in the experiment on castrate hyperthyroid animals, in that there was no significant difference in the gonad-stimulating power of the hypophyses of such animals when compared to castrate controls. Theelin, as a modifying factor, was eliminated in this experiment by castration, so if the thyroid were able to effect the hypophysis directly, it seems probable that such an effect should have been manifested.

The action of anterior pituitary extracts also does not seem to be affected by the hyperthyroid condition. The fact that the gonad-stimulating power of the hypophysis increases in castrated hyperthyroid rats is a priori evidence that the effects of injections of hypophyseal extracts may not be affected by a hyperthyroid condition. In the experimental work it was found that hyperthyroid animals which received a total of 0.25 gram equivalent of dried anterior pituitary powder did not show an oestrous condition. This might be taken as an indication that the thyroid was able to eliminate small amounts of the hypophyseal hormone. However, it seems more probable that the best explanation of this is that under the influence of 0.25 gram equivalent of the pituitary powder, the ovary did respond, but enough thyroid substance was present to inhibit the action of sufficient follicular hormone to keep its amount below the threshold required for the production of oestrus. When the animals received larger doses of the hypophyseal extract, a correspondingly greater ovarian stimulation occurred, with the result that enough theelin was produced to reach, in spite of its rapid elimination due to the thyroid present, the threshold value required to produce oestrus. The distinct increase in the weight of the ovaries of the animals treated with anterior pituitary extracts, as compared with normal animals treated with the same extract, suggests the fact that the activity of this extract was not affected by the presence of a large amount of thyroid substance. When the pituitaries of such hyperthyroid animals were transplanted into immature female rats, they did not produce any more stimulation of the ovaries than the control. It seems quite likely that in this case the theelin produced by the ovary under the influence of one gram equivalent of dried pituitary powder was capable of decreasing the potency of the animal's pituitary.

SUMMARY

In determining the effect of an excess amount of thyroid substance on the physiological activity of theelin it was found that in 20 out of 24 castrated female white rats in a hyperthyroid condition, approximately three rat units of theelin were necessary to produce artificial oestrus.

Twenty-four female rats of uniform weight and normal oestrous cycles were fed 900 mgm. per kgm. of body weight per day of desiccated thyroid powder. After six weeks of feeding, the animals having remained in a dioestrous condition for a period corresponding to at least four normal

cycles, their hypophyses were implanted into sexually immature female rats. Control hypophyses were implanted into litter mate sisters of the experimental recipients. After five days the ovaries were weighed. It was found that the hyperthyroid condition caused an increase in the gonad-stimulating power of the hypophyses ranging from 15 to 63 per cent.

Hypophyseal implants from hypothyroid female adult rats, made five weeks after complete thyroidectomy, showed little change in gonad-stimulating properties beyond controls.

Hypophyseal implants from 12 ovariectomized rats, fed thyroid as outlined above, showed no significant increase in gonad-stimulating properties.

Gonad-stimulating extracts of sheep anterior pituitary, when injected into both hyperthyroid and normal adult rats in varying doses, caused a distinct increase in ovarian growth in all cases.

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RAT SEMINAL VESICLES AND PROSTATE GLANDS AS QUANTITATIVE INDICATORS OF TESTICULAR HORMONE*

IRA BOWERS HANSEN
From Hull Zoological Laboratory, University of Chicago
CHICAGO

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I. INTRODUCTION

A study of the reactions of both seminal vesicles and prostate glands of rats was undertaken to determine their usefulness as quantitative indices of the presence of testicular hormone. It was known that both glands responded distinctly to castration with a definite histology that differed widely from the normal condition in those organs. It became desirable to know whether either or both glands would respond quantitatively to different concentrations of injected male hormone, and whether they would respond constantly enough so that they might be relied upon to be used as an assay method.

In the extraction of testicular hormone, active material is obtained, in a form as pure as possible, by successive treatments that eliminate inactive organic substances. The strength of activity, as well as the determination of the presence of activity in a solution, thus far can be indicated only by biologic tests. In the absence of chemical or physical tests for the estimation of the amount of active male hormone present in a sample, it is necessary to develop biologic tests that by their accuracy may be of distinct service to the physiological chemist or to the experimental worker who desires to know the strength of the male hormone he wishes to use. Thus far the chief criterion for such a purpose has been the capon comb, a quantitative method developed by Gallagher and Koch (1930).

The capon comb method is one that depends upon a reaction in the bird to substances extracted from mammalian tissues, and is thus far the most satisfactory method developed for assay. Suitable quantitative methods using the mammal as the test animal, however, are also desirable from several points of view. The comb growth reaction, though the most de-

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pendable assay method yet developed, is surrounded by certain features of a somewhat disconcerting nature. Further, radically different biological reactions may be important in determining the character of materials subjected to analysis. Thus both extracts of bull testes and extracts of male urine stimulate growth of the capon comb. Probably the same substance is obtained from both sources, but due to a slight uncertainty that it is so, analysis by bird and mammal reactivity would be desirable. It is also true that the maintenance of a proper group of capons for assay purposes is attended, perhaps, with greater difficulty and expense, at least in some localities, than is that of small laboratory animals. With these points in mind a study has been made of certain accessory reproductive organs in the rat to determine their applicability to the quantitative assay of the testis hormone.

In order to develop a quantitative method, it was necessary to find some tissue or organ that depends upon the testicular hormone for its normal activity and structure, and at the same time responds very definitely to castration. This requirement was easily filled by the rat seminal vesicles and prostate glands, the reactions of which to castration and to hormone injections had previously been extensively studied and reported by Moore, Hughes and Gallagher (1930) for the seminal vesicles, and by Moore, Price and Gallagher (1930) for the prostate.

To review briefly the situation as previously described, it can be said that the normal paired seminal vesicles of the rat are lobulated, elongated, sac-like glands that have a main central chamber running the entire length of the gland, from which diverge numerous side branches. The glandular epithelium is one cell in thickness, and the cells are of a tall columnar variety. The most conspicuous feature of the cytoplasm of these cells is the presence of secretory granules, usually numerous, between the basal nucleus and the distal end of the cell. These granules are characterized by the presence of encircling halos.

Following castration, Moore, Hughes and Gallagher (1930) point out that the enhaloed secretory granules disappear within forty-eight hours, and that a progressive diminution in the height of the epithelium takes place until the cells are of the dimensions of the nucleus. Macroscopically there is likewise a decrease in the total size of the seminal vesicles, and a loss of secretory ability. These regressive involutionary changes have been stopped and a completely castrate gland rebuilt to the normal structural and functional state by the injection subcutaneously of extracts of bull testes. This definite reaction of the seminal vesicles to castration and their response to the presence of testicular hormone constitutes one of the major qualitative tests for male hormone.

In like manner, Moore, Price and Gallagher (1930) have described the normal prostate and its reactions to castration. The normal rat prostate consists of three lobes—anterior, middle, and posterior. The anterior portion is divided into a right and left lobule which is located on the posterior

margin of the respective left and right seminal vesicles. The anterior portion of the prostate is different histologically and physiologically from the middle and posterior lobes, which are identical. Since in the present study, the anterior prostate was omitted from consideration, it is pertinent only to indicate the normal and castrate conditions of the middle and posterior lobes.

The prostate is a typical acinous gland consisting of a number of convoluted alveoli supported by a stroma of loose connective tissue. In the normal condition the lining epithelium consists of a single layer of high columnar cells with basal nuclei. These cells are characterized by the presence of a light area in the distal portion of the cytoplasm between the nucleus and the outer cell wall. These light areas in the cells of the epithelium give the appearance under low magnification of a light band between the deeply stained nuclei and the cell border.

After castration it was pointed out that the light areas disappeared from the cells within five days, and that there was a definite loss in epithelial height. Besides these changes, there was a decrease in the size of the acini, and a decided increase in the amount of interacinous connective tissue. All these castration effects could be eliminated or prevented by the injection of extract of bull testicles. These reactions constitute a second qualitative test for the presence of male hormone.

With such adequate information available, it was quite obvious that the two glands gave a range of characteristics, not only in the number of different things responding to the lack of male hormone, but in the degree to which they reacted. To make use of them in a quantitative study it remained to discover what was the basal level following castration, how soon that basic condition developed following the removal of the gonads, whether it was more advantageous to inject immediately after the operation of gonadectomy, and lastly, what the quantitative responses might be in the tissues studied.

II. MATERIAL AND METHODS

To determine how soon the castration changes had become maximum and uniform, rats were killed at periods ranging from five days after castration, through ten, fifteen, twenty and sixty days following castration. It was found that seminal vesicles and prostates of five-day castrate rats had not completed the involutionary changes following the removal of the testes. It was likewise true that after ten days the histologic picture was not that of the basic level obtainable by longer periods of castration. At the end of fifteen days the histologic picture was decidedly castrate in the majority of animals. Complete uniformity was obtained after twenty days. Beyond that point there was a very small further change which was of no material importance. A sixty-day castrate does not differ noticeably from a twenty-day castrate, although a one hundred twenty-day castrate does show further decrease in size of cells beyond that shown in the twenty-day

castrate. The greatest involution, however, occurs safely within the first twenty days, and the stage reached at the end of that time may be used as a basic castrate condition upon which to rebuild the epithelium by hormone injections if so desired.

It was next necessary to discover whether it was advisable to start the injections immediately after castration, or following the assumption of the basic castrate condition, or at some time in between. The possibility existed that the length of time intervening between the gonadectomy and the beginning of injections would have a bearing upon the rapidity and the amount of response in both the seminal vesicles and the prostates. Likewise the question as to the number of daily injections to be given in order to get the most uniform picture among the animals had to be answered. Five animals were arbitrarily chosen as the minimum number to be used for the assay of any particular sample, and experience has shown that not fewer than five can be used without the sacrifice of some accuracy.

A preliminary group of animals was castrated and divided into four categories. Those in group A were permitted to remain ninety days before injections were started; group B for twenty days; group C for ten days; and a group D for only one day. Each group in turn was divided into two classes, one receiving ten consecutive injections, and the other receiving twenty consecutive daily injections. Each animal received one-half cc. injection daily of seven to eight bird units. This study indicated that the longer the time elapsing after castration, the longer time did it take to rebuild the gland. This was well shown in a comparison of the ten-day castrates with the ninety-day castrates. Likewise, there was good evidence to show that there was greater variation between the histologic pictures of the glands after twenty injections than after ten, a fact which probably can be explained upon the basis of poorer absorption as the amount of oil under the skin increases with added injections.

As a direct outcome of this preliminary study it was decided that ten daily injections beginning the day after castration, the so-called "maintenance procedure," gave less variable results, and was advantageous in that it reduced the time requirement for the total procedure, required less total hormone, and did not demand a stock supply of castrated rats.

The method that has been followed throughout this whole study, therefore, is as follows. Rats castrated were injected once daily beginning the day following the operation, for ten days with one-half cc. of the hormone sample. Upon the eleventh day they were killed and the seminal vesicles and prostates recovered. Before removal from the animal, the seminal vesicles were measured carefully with calipers and their condition noted as to turgidity and the presence of secretion. Fixation was in Bouin's solution. The tissue was cut at four micra and stained in Erhlich's hematoxylin without counterstain.

Subsequent to the decision on a method of procedure, twenty-two samples of male hormone derived from bull testicular extracts and carried in

olive oil have been injected into batches of five animals each. Eighteen of these samples were dilutions of the same hormone stock. In addition two blanks consisting of pure olive oil have been injected, which constitutes in total the utilization of one hundred twenty rats. There has been no attempt to use inbred strains other than exists in a mixed colony maintained for purposes of reproduction. Rats that were used varied in weight from 170 to 380 grams.

III. QUANTITATIVE REACTIONS OF THE SEMINAL VESICLES

Macroscopically, the seminal vesicle responds to castration by becoming very flabby, decreasing in size, and by losing its power to secrete. This is in marked contrast with the normal gland which is usually turgid, distended, and full of coaguable secretion. Such obvious changes are qualitative criteria for the presence or absence of testicular hormone, but practically useless as a means of quantitative estimation of the amount of hormone the animal is receiving in its daily injections. There is a tremendous variation in the size of seminal vesicles in normal rats, so much so that size alone is of no use to indicate hormone concentrations. The size of the seminal vesicles has been carefully followed in an attempt to correlate the length-breadth index with the hormone strength, but the results are discouraging. Table I indicates the variation encountered in this method for the rat. The positive correlation between the bird units injected and the length-breadth index is 0.51.

TABLE I

Bird Units Injected	Length x Breadth of Left Seminal Vesicle
0.09	81.9
0.29	75.0
0.50	69.2
0.58	75.6
0.96	85.1
1.10	82.7
1.41	80.7
1.55	67.3
1.65	103.6
2.00	91.8
2.25	92.2
2.25	70.5
2.50	83.5
3.75	102.3
3.75	87.1
4.14	91.5
5.00	83.9
5.50	97.2
10-day castrate.....	70.9

Presence or absence of secretion, however, may serve as a general guide at the time of killing. Gentle pressure upon the gland after cutting from the animal may or may not result in the exudation of a secretion from the open lumen. If secretion does appear it may be watery or it may be viscous. Viscous secretion has been noted to be present in seminal vesicles after the injection of 1.65 bird units in all of the animals. Below that concentration secretion may appear in a single animal of a group but it is

always very watery and very scant in quantity. Microscopic examination shows some type of secretion to be present in the lumina of all vesicles, whether from castrates or from heavy injections, although varying in amount and in quality. That in a castrate is very fibrous, thin looking, and pale staining, and probably is a deterioration product of the secretion present before castration. In contrast, that from an animal receiving injections of 2.25 bird units shows a solid colloid more heavily staining with hematoxylin, a product of continued secretory activity. Microscopic examination for colloid is useless for a quantitative estimation of the units of hormone injected, while macroscopic examination seems to be good to indicate either a relatively high concentration, or a relatively low one.

In a consideration of the reaction of the seminal vesicle to varying concentrations of testicular hormone, there are certain cytologic characteristics which respond quantitatively and have been used to distinguish one dilution of hormone from another. The most obvious of these is the epithelial height. The epithelium of the normal rat seminal vesicle is of the tall columnar variety with an average height of eighteen to twenty micra. The cells are very narrow, about the width of the basally situated nucleus. Castrated animals, however, show an epithelium which in height is scarcely more than that of the nucleus. There is a range, then, from the castrate type (about 8.4 micra in the ten-day castrate) to the normal type of twenty micra.

For every sample assayed the average epithelial height has been determined by measuring with an adjustable ocular micrometer sixty cells in a random section for each animal. Five animals, then, permit a point based upon three hundred measurements, which is as accurate as the variability of the tissue will allow. Care was exercised to measure regions of the gland that were not distended by large amounts of secretion, and cells that were cut as nearly as possible in a plane parallel with the long axis of the particular cell. Table II and the graph of the seminal vesicle show clearly the results in summary form. There is a positive correlation between the

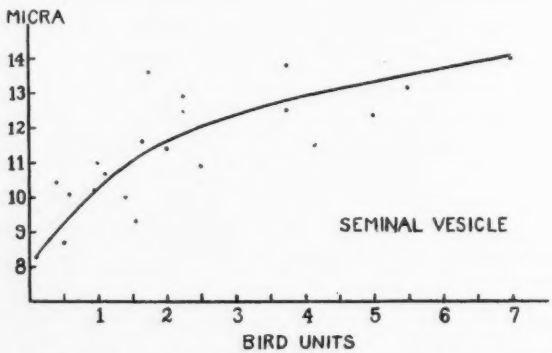

Figure 1. Correlation between Epithelial Height in Micra and the Strength of Hormone Injected in Bird Units for the Seminal Vesicle.

TABLE II
SEMINAL VESICLES

Bird Units Injected	Epithelial Height in Micra
0.09	8.3
0.29	8.8
0.40	10.4
0.50	8.7
0.58	10.1
0.96	10.2
1.00	11.0
1.10	10.7
1.41	10.0
1.55	9.3
1.65	11.6
1.75	13.6
2.00	11.4
2.25	12.9
2.25	12.5
2.50	10.9
3.75	12.5
3.75	13.8
4.14	11.5
5.00	12.4
5.50	13.2
7.00	14.0
10-day castrate	8.4
178-day castrate	7.2
Normal rat	20.0

strength of hormone injected and the epithelial height of 0.72 with a probable error of 0.069.

Another criterion that is of service in the estimation of the weakness or strength of hormone is the presence or absence of secretory granules. The cells of the normal seminal vesicle epithelium contain distinct secretory granules in the distal portion of the cells, and each of these granules is surrounded by a characteristic clear ring or halo. Castrated animals, however, have lost these granules possessing halos, and in this regard again present a distinctly different cytologic picture from the normal. Granules without halos have been shown to be present in seminal vesicles after receiving ten injections of a sample of 0.5 bird unit. These fine granules are difficult to see, and are of doubtful value to the assay. Granules showing halos are of service since they are differentiated from the ordinary granular cytoplasm, and it is these that are looked for in the determination of the strength of the sample. These were first noted in a small percentage of cells after an injection of 1.1 bird units. Granules increase in number and in strength as the concentration of the injected hormone is increased. This may be indicated roughly as shown in Table III.

TABLE III

Bird Units	Granules
1.10	– Small in size, few with tiny halos
1.41	– Weak, with tiny halos
1.55	– Weak, with few tiny halos
1.65	– – Weak, small halos
2.00	– – Weak
2.25	– – – Good, numerous
2.50	– – – Good, numerous
3.75	– – – – Very distinct and numerous
4.14	– – – – Very distinct and numerous
5.00	– – – – – Strikingly clear
5.50	– – – – – Strikingly clear

Granules are difficult to estimate quantitatively with any accuracy, but may be used to place an unknown sample in the general range of concentration.

Taking all the criteria into consideration, it is found that the seminal vesicle may be used as a quantitative index of testicular extract injections. It is available for assay of dilutions from about 0.4 bird unit up to approximately 7.0 bird units. The more accurate range of the seminal vesicles is considerably narrower and lies between 0.4 and 2.5 bird units. At higher concentrations the assay becomes less dependable.

IV. QUANTITATIVE REACTIONS OF THE PROSTATE GLAND

In this consideration it is to be borne in mind that the anterior lobe of the prostate (the "coagulating gland") does not enter into the discussion. Only the middle and posterior lobes have been followed, and the description belongs to their behavior. They have been treated as identities which seems strictly to be the case.

Macroscopically, the prostate in the normal rat is turgid, large, and full of secretion. Upon castration, changes occur which result in a smaller, darker colored gland without secretion. Usually there develops an abundance of fat upon and around the surface of the castrate prostate, a feature which is missing in the normal rat. Such changes are useful as a very general indication of the state of the hormone condition, but no more than that.

The prostate has a very characteristic cytology which is of use in an assay. The normal cells are tall columnar and are striking because of the presence of circumscribed light areas, or light spots, in the distal end of the cells. These areas stand out distinctly in contrast to the remainder of the granular cytoplasm. After castration these light areas totally disappear. There is, likewise, a concurrent involution of the epithelium resulting in a low cuboidal cell layer. Cells which normally average thirty-one micra drop in height to sixteen micra. With these castration changes there is a positive increase in the amount of connective tissue stroma between the acini of the gland. In regard to the stroma, the connective tissue response has not proved to be capable of more than a suggestive indication of strength. It is obvious, however, that it is only when the injected dose is well below one bird unit that the connective tissue stroma increases, and then not markedly until almost no hormone is administered. A very little testicular hormone is able to prevent the increase of connective tissue, although it may not keep the whole gland functional.

The prostate shows a reaction to low dosages of hormone that is rather difficult to record. Invariably it is found that the acini along the periphery of the glandular mass will respond first, and give a strong reaction while the rest of the gland remains castrate in all appearance with the exception of the amount of connective tissue. This response, then, is not uniform throughout the whole gland, but in weak concentrations shows itself in

only a relatively few acini. Likewise, in animals receiving relatively strong doses, the same difficulty prevails, due, however, to a different cause. Here the factor of distention plays a large rôle. An acinus that is distended with its secretory product will be found to be bordered by a lining epithelium of a cuboidal nature, in some cases still showing light areas, and in other cases without light areas and precisely similar to the cells found in an untreated total castrate. To take an average height of the epithelium as was done for the seminal vesicle is practically of no avail. To make an estimation of the percentage of cells, or acini, showing a definite reaction to the amount of non-reacting tissue can be done, but it is found that such a ratio in one animal will vary widely from the ratio in the second, a result which is most unsatisfactory where both animals are receiving the same concentration of testicular hormone. Further, the percentage of reacting tissue seems to bear little correlation with the hormone dosage.

To make some sort of estimation it has been found useful to measure the highest rather than an average epithelium. This method gives an indication of the strength of reaction in those portions of the gland which are actively responding. Ten measurements per gland have been taken of the highest epithelium available, and these measurements in turn averaged for each batch of five animals. The results are shown in Table IV and pictured in the graph. The positive correlation between the height of the cells as measured, and the strength of hormone injected, is 0.78 with a probable error of 0.056.

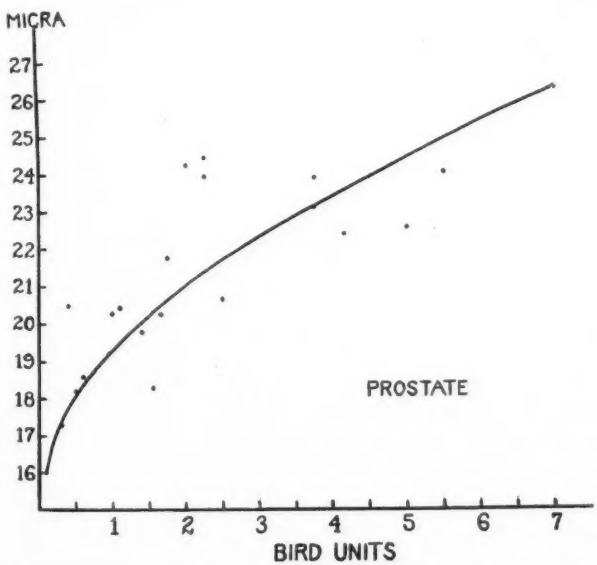

Figure 2. Correlation between Epithelial Height in Micra and the Strength of Hormone Injected in Bird Units for the Prostate Gland.

TABLE IV
PROSTATE GLAND

Bird Units Injected	Epithelial Height in Micra
0.09	16.0
0.29	17.3
0.40	22.6
0.50	18.2
0.58	18.6
0.96	19.2
1.00	23.3
1.10	22.3
1.41	19.8
1.55	18.3
1.65	20.3
1.75	21.8
2.00	24.3
2.25	24.5
2.25	24.0
2.50	20.7
3.75	24.0
3.75	23.2
4.14	22.5
5.00	22.7
5.50	24.2
7.00	26.5
10-day castrate	15.9
Normal rat	31.0

Tissue which shows no light areas at all must be relegated to the castrate category, not because it is impossible to distinguish it in many cases from a typical twenty-day castrate, but because it is impossible to separate it from a ten-day castrate, the control period for these experiments. It was found that a ten-day castrate prostate shows variations in epithelium height sufficient to make it impossible to decide between a very low concentration of hormone (0.09 bird unit) and the castrate type itself. The weakest dose that has thus far been observed to produce light areas is 0.29 bird unit, but it is believed that they will appear at lower concentrations than that.

In general, as the hormone strength increases there is a progressive increment in the number of acini reacting until even the distended acini will show cuboidal epithelium containing distinct light areas. These light areas first appear weak, more easily seen under lower magnifications than under oil immersion, and then increase in contrast, in sharpness, and in size until they are strikingly obvious even under oil. The assay range of the prostate is rather short, for beyond 1.5 bird units the response begins to approach a maximum that does not permit clear distinctions; for example, between a hormone strength of two bird units and one of four bird units.

V. APPLICABILITY OF THE METHOD

After the method of procedure had been established, twenty-two hormone samples plus two blanks of pure olive oil were injected into rats as unknowns. Although previously carefully assayed in bird units by Dr. T. F. Gallagher, the values were kept secret until a report was made both placing the unknowns in their relative order of strength, and assigning a value to them upon the basis of the reactions of both seminal vesicles and

prostate glands. This prevented any prejudice or any preconceived notion of what the tissue should be like from entering into the actual judgment and calculation. It also indicated roughly how useful and how dependable for an assay were such criteria as have been described. The first series of five unknown samples were merely placed into order according to the relative strength of hormone as indicated by the tissue reactions of the seminal vesicles and prostates. This proved easy to do since the five samples were wide in concentration range, and in actual values were 1.1, 2, 3.75, 5.5 bird units and one blank of pure olive oil.

With these four points established, another series of five unknowns were injected and a report made with reference to their relative strengths and estimated concentrations in bird units. Since nothing lower than 1.1 bird units had previously been given, those doses reported in bird units below that were largely chance judgments with the exception that they were definitely weaker than 1.1 bird units. They were again placed in the correct order of strength. A comparison of actual value and estimated value may be made in the following table.

SERIES 2

Actual Value in Bird Units	Estimated Value in Bird Units
0.00	0.3
0.58	0.7
0.96	0.9
1.65	4.0
2.25	4.5

The procedure was repeated with five more unknowns, now using the additional data acquired as further reference points. Again the correct order was reported for the concentrations, and can be summed up in the following table. It will be noted that 2.25 bird units appears in both series 2 and series 3, and were portions of the same sample.

SERIES 3

Actual Value in Bird Units	Estimated Value in Bird Units
0.09	0.00
0.29	0.75
1.41	0.98
2.25	4.50
3.75	6.70

Series 4 is a repetition of the same procedure, using unknown samples, and with the use of previous experience, attempting to estimate the concentration in bird units. Again the samples were easily placed in order according to strength. This has proven to be true of all series thus far injected.

SERIES 4

Actual Value in Bird Units	Estimated Value in Bird Units
0.50	0.25
1.55	0.60
2.50	1.70
4.14	3.00
5.00	4.00

With the last group of animals into which four unknowns were injected, it was anticipated that a good estimation might be obtained of the actual adaptability of the seminal vesicles and prostate glands to use for an assay. Unfortunately the whole group of rats, during the course of the injections, became very sick with dysentery, and the results, therefore, are affected by the factor of ill health and do not represent the full potentialities of this method as an assay. The estimation and actual values are given in the following table.

SERIES 5

Actual Value in Bird Units	Estimated Value in Bird Units
0.40	1.4
1.00	1.8
1.75	5.7
7.00	6.5

VI. DISCUSSION

As a quantitative method, the several criteria of the seminal vesicles and prostate glands, taken separately or considered in the aggregate, are adaptable to use for an assay. Just as is the case with a large number of biologic assays depending upon the numerous uncontrollable factors running rampant in the living organism, the desired precision is still lacking and it is somewhat doubtful whether it will ever be attained much beyond its present status. It is assured that both the prostate and seminal vesicles react not by any "all or none" response to a requisite threshold, but in direct proportion to the amount of stimulating hormone present. Such a sensitivity to the presence of the existing agent is the fundamental property that permits of an assay based upon those tissues. It was shown by Moore and Gallagher (1930) that there was such a relationship existing for the prostate and seminal vesicles, and further, that there was a corresponding relation in the response of the Cowper's gland and the vas deferens. They brought out the minimum hormone threshold relationships between the various accessories and indicated clearly that the most sensitive, the organ responding to the least amount of testicular hormone, was the prostate and that this was followed in turn by the seminal vesicle, Cowper's gland, and finally the vas deferens with the highest hormone threshold.

This present study is able to corroborate fully the threshold relations of the seminal vesicle and the prostate. It has been shown that the prostate will react to exceedingly minute amounts of testicular extract. A bird unit of bull testicular hormone is equivalent to approximately 0.01 mgm. of solid active material (Gallagher and Koch, 1929). Nevertheless, characteristic light areas have appeared in some of the cells with a dose as low as 0.29 bird unit (daily injection of 0.002 mgm. of gross solids), and it is probable that the light areas can be produced by smaller injections than this. They did not appear after the injection of 0.09 bird unit, although the requisite epithelium height was sufficient to permit their appearance. The seminal vesicle, upon the other hand, shows but little response until 0.4 bird unit has been employed, and then the reaction consists merely in an increase in the cytoplasm with the concurrent increase in height of the epithelium. This condition is not a functional one by any means, nor are any of the cells in the gland in a functional state. This is in contrast with the prostate where it is believed that light areas are indicators of physiological function. Slight functional ability as indicated by secretory granules with halos appears about 1.1 bird units.

A further contrast between the seminal vesicles and the prostate is strongly brought out by the amount of hormone necessary to produce a healthy, functional gland. Two bird units will do it easily for the prostate, while about six to seven are needed for the seminal vesicle. It should be pointed out that while such dosages do produce a functional gland with the cytologic picture of the normal, it does not reproduce the epithelial height of the average normal rat. With the concentrations of testicular hormone used (up to seven bird units), it has proved impossible to duplicate the height of the epithelium of either the normal prostate or the normal seminal vesicle. This seems a little hard to explain when it is not necessary to rebuild an epithelium within ten days, but merely to sustain it, unless we logically admit that the average normal rat is producing greater than seven bird units per day.

Heller (1932) injected various concentrations of testicular hormone into castrate rats in the attempt to find what direct relationship there might be between hormone concentration and reaction of Cowper's gland. His table of data and the accompanying graph indicate quite clearly that there is a positive correlation certainly, but the gland is too slow in reacting, and too variable to serve as an assay method. He apparently was successful with either six or seven bird units in restoring the minimum normal height of twenty-nine micra, but never succeeded in reaching the upper range of thirty-two micra.

Moore and Gallagher (1930), after carefully studying threshold relationships of the accessories to testicular hormone, defined the rat unit in terms of complete gonadal substitution. They stated, "A rat unit of male hormone is defined as that minimal daily amount required to maintain fifty

per cent of castrated animals in normal condition," and stipulated that the indices of the normal condition be the normal prostate and seminal vesicle. At that time it was suggested that one rat unit was equal to approximately six bird units. Although this present study seems to indicate that six bird units is a bit too low an estimate for complete replacement of epithelial height, it nevertheless is not far in error.

The results of this study, obviously somewhat incomplete, do not especially recommend it in preference to the capon comb growth method. The latter method is easy to apply, and the assay is readily obtained by the simple measurement of the comb growth. Further, the same animals can be used again for subsequent assays as they are not sacrificed. The chief unfortunate features lie in the difficulty of performing a successful operation which will leave the capon permanently without testes, and in the care and space that chickens require in order not only to maintain a colony, but to keep the birds healthy. Upon the other hand, rats are available for use in nearly every laboratory, castration is rapid and sure, and the animals withstand surgical treatment without difficulty. There is the distinct disadvantage, however, that the experimental animals have to be sacrificed to make the assay, and that there must intervene the routine technique of fixing, sectioning, and staining, before the tissues can be studied. This is a handicap to speed, and although smaller amounts of hormone can be detected than by the use of the capon comb further work is necessary before one is justified in claiming great accuracy in assay. There may be further justification for the rat method in that a mammal is used as the test animal for a mammalian tissue product.

Other methods for indicating quantities of male hormone have been suggested. Funk, Harrow and Lejwa (1930) suggested a cock unit depending upon the reactions of capons. Their cock unit is defined as "that amount of male hormone which, when injected, will increase the size of the comb and wattles to the extent of 10 mm. in 10 days." Six animals are used for each test, and an average reaction taken. Schoeller and Gehrke (1931) also defined a bird unit depending upon the capon comb reaction, and Freud, de Fremery, and Laqueur (1932) have added still another bird unit depending upon the capon comb.

Muto (1928) suggested that the weight of the seminal vesicles in the mouse be used as an index for testicular hormone, since there is a decided difference between the normal condition and that following upon castration.

Martins and Rocha e Silva (1930) indicated that a more useful index of hormone concentration might be found in the utilization of measurements of the mouse seminal vesicle. They measured the length and the breadth, and derived a length-breadth index by multiplying the two together. In the normal eighteen-gram mouse, the index varies between fifty-two and ninety-two. Ten days after castration the index is as low as

twenty and sometimes as low as ten. After hormone injection they were able to build a seminal vesicle with an index of sixty. The range between twenty and sixty should serve for an assay method.

Loewe and Voss (1930) in a review article, outline their "cytologic regeneration" test for male hormone. Voss and Loewe (1931) give further information. They indicate that macroscopic relations of the mouse seminal vesicle are too variable for an assay method, but devote their energies to a microscopic determination. Following a previous castration period of four weeks, the mice are injected three times in thirty-six hours and killed one hundred hours after the first injection. For an assay they depend upon secretion granules and vacuoles, cell height, new mitotic figures, secretion in the lumen, and the condition of the chondriosomes. In the 1931 paper they publish an interesting graph plotting the correlation between the secretory granules and the length-breadth index. They roughly classify the granular condition into five categories, granules in all cells, in most cells, in one-half of the cells, in a few cells, and in no cells. This curve, then, can be but approximate and depend very largely upon personal judgment of the investigator. The cytologic regeneration test is an interesting one, and closely associates itself with the present study upon the rat. Just how precise the mouse test is, is not known to this author.

Lendle (1931) has attempted to make use of the anti-feminine reaction to establish a standard quantity of male hormone. The amount of male hormone necessary to suppress the oestrous cycle in female rats is the unit involved. Ihrke and D'Amour (1931) also showed clearly that injection of male hormone would suppress the oestrous cycle, but made no attempt to use such information as a measure of hormone strength. There appears to be one difficulty at least in the way of a safe assay thereby, and that lies in the fact that many factors will affect oestrous, and particularly the injection of organic impurities.

Glaser and Haempel (1931), working with fish, announced a method to standardize male hormone by injecting it into a fish, Rhodeus amorus, which had been castrated thirty days or more in advance. Within four to five hours after injection there is an intense red coloration of the fish. This method has the advantage of a five-hour standardization, but again probably is not very precise. This far only a note has been published concerning the reaction.

Even though male hormone has been produced in crystalline form by Butenandt (1932), there still is interest in a quantitative assay method. For the mammals thus far, only the method of Loewe and Voss, and the present study seem to give promise. Both are similar, with the exception that by the use of both seminal vesicles and prostate glands a wider range for assay is obtained, smaller dosages of hormone can be determined, and the two glands serve as a check upon each other.

VII. SUMMARY AND CONCLUSIONS

In a study of the applicability of rat seminal vesicles and prostate glands to the assay of testicular hormone, it was found that both structures gave quantitative reactions that might be used as criteria of hormone strength. The indices of the seminal vesicle were the presence of secretion, cell height, and the presence of secretory granules with halos. For the prostate, epithelial height and the presence of light areas proved satisfactory. In a comparison of the prostate and seminal vesicle it was shown that the prostate was the more sensitive with an accurate assay range from about 0.15 bird unit up to 1.5 bird units. The seminal vesicle indicated an assay range varying from 0.4 bird unit up to approximately 7.0 bird units. By using both glands in combination the assay range extended from 0.15 bird unit to 7.0 bird units. These conclusions are based upon the assay of 24 samples that had been previously assayed in bird units.

A method of procedure was developed for the assay of testicular hormone. This consisted in total castration of five rats upon one day and injection subcutaneously of one-half cc. daily of the unknown sample, beginning the day after operation, for ten successive injections. Upon the eleventh day the animals were killed and the seminal vesicles and prostates recovered. Tissue was fixed in Bouin's, cut at four micra and stained in Ehrlich's hematoxylin without counterstain.

This problem was suggested by Dr. Carl R. Moore, and it is with much gratitude that his advice, guidance and assistance are acknowledged. The extracts of bull testicles employed in this study were prepared by Dr. T. F. Gallagher under the direction of Professor F. C. Koch in the Department of Physiological Chemistry and Pharmacology, and had been previously assayed by Dr. Gallagher in bird units. It is indeed a great pleasure to acknowledge to them my indebtedness for the material and cooperation in this work.

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IRREVERSIBILITY IN ADRENAL INSUFFICIENCY*

FRANK A. HARTMAN AND CHARLES A. WINTER
From the Department of Physiology, University of Buffalo
BUFFALO

In our earlier work (Hartman, Griffith and Hartman) with cortin, we observed that "If the animal reached the stage of prostration, the injection of cortical extracts was useless in most instances." Whether this was due to inadequate dosage or to some irreversible change in the organism was not determined. It has since been shown that large amounts of cortin, especially if frequently administered, may revive animals in the stage of prostration (Hartman, Brownell and Hartman; Pfiffner and Swingle). However, this does not always succeed. In Addison's disease, likewise, failure sometimes occurs (Hartman, Thorn, Lockie, Greene and Bowen). In the latter we could not be sure that an adequate amount of hormone was given. For this reason a study of the question in animals was desirable, because relatively large doses could be administered and conditions could be better controlled.

We have used cats, guinea pigs and monkeys (Macacus rhesus) in our study.

The adrenals have been destroyed or removed in two stages. In the guinea pig electric cauterization proved to be more satisfactory than ligation. Curved forceps were held beneath the gland to prevent excessive bleeding while cauterization was in progress. The gland was cauterized and removed piecemeal. Care was necessary to avoid injury to the vena cava. In the cat and monkey the adrenals were ligated and cut out.

All operated animals were kept in a constant temperature room maintained at about 27° C.

Extracts of cortin were used that were also being tested in adrenalectomized rats or cats.

Extracts containing the product of 40 gm. of cortex or 60 gm. of whole adrenal per cc. were employed. Injections were made twice daily unless otherwise stated.

Some of the guinea pigs were exercised in a motor-driven treadmill of the horizontal belt type.

The experiments cited have been chosen from a larger series of animals used in the study of the function of cortin. They include instances of death which occurred without premonition of a serious condition.

We have revived cats, rats and guinea pigs from the prostration of adrenal insufficiency produced spontaneously or by such stresses as exer-

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cise or toxins (Hartman and Scott). The following is a protocol of a guinea pig revived from one prostration of adrenal insufficiency produced by exercise.

Protocol 1. A male guinea pig (No. 7) weighing 575 grams had its adrenals destroyed in two stages nine days apart. One cc. of extract twice daily was not adequate at first, so this dose was doubled at the end of 13 days. At 30 days the injections were reduced to 1.5 cc. At 50 days the animal was exercised for 1 hour and 48 minutes, traveling 3487 feet. Extract was discontinued until the animal became prostrate at 58 days. He was then given 4 cc. half intraperitoneally and half subcutaneously. Within 30 minutes the animal was standing but was hyperexcitable. At 1 hour 4 cc. more was injected subcutaneously. At 2½ hours the animal was shivering and very weak; 2 cc. of extract was injected. At 4 hours he appeared better; 1.6 cc. was injected. He continued to improve on 2 cc. twice daily. After a few days the dose was reduced to 1.5 cc. and then 1 cc. at each injection. One cc. seemed to be the minimum maintenance dosage, for with 0.8 cc. he lost, but with the former he gained weight. Later he succumbed to adrenal insufficiency brought on by inadequate dosage.

He was gaining weight so slowly at 2.0 cc. per day that the dose was increased to 2.4 cc. daily. An untried lot of extract was injected. This was followed by a loss of weight. On the 187th day the dosage was increased to 3 cc. daily of tested extract. On the following day convulsions developed. Three cc. of extract was administered intraperitoneally following the convulsions but the animal remained prostrate. Injections were made at intervals until an additional total of 5 cc. intraperitoneally and 1.8 cc. subcutaneously had been injected. In spite of this the animal died 1 hour and 24 minutes after the onset of convulsions. The stomach and intestines were hemorrhagic.

This animal is typical of those revived from prostration. Frequent injections of cortin are required until the critical stage is past. During the day of the first crisis the guinea pig just described was given about four times the maintenance dosage required after complete recovery. Perhaps less would have sufficed. At the last crisis not quite this amount of extract was administered in less than two hours without improvement.

So far as we know the use of cortin has not been previously studied in guinea pigs. Five animals, which we have carried 50 days or longer after complete destruction of the adrenals, required 3 cc. of cortical extract divided into two doses as a daily maintenance dose. On the other hand, one young guinea pig (520 gm.) died 21 days after adrenalectomy with 4 cc. of cortical extract daily.

It has not always been possible to bring about recovery from adrenal insufficiency in guinea pigs with large amounts of extract as the following protocol will show.

Protocol 2. A male guinea pig (No. 2) had its adrenals destroyed by cautery in two stages nine days apart. It weighed 402 gm. at the time of the second operation (42 gm. increase over the first operation). Injections were made twice daily, the amount of extract being varied from time to time, the dosage ranging between one and two cc. of cortical extract daily. This animal seemed to require 2 cc. daily. He was doing well and had attained a weight of 652 gm. on the eighty-third day when he was placed in the treadmill. He traveled a distance of 1727 feet in 29⅔ minutes. He was given 2 cc. of extract 2 hours before the exercise. A similar dosage was repeated at 1½ hours, 2½ hours, 4 hours, and 7 hours after the exercise. Although showing symptoms of acute adrenal insufficiency following the exercise, he became much improved after the injections. The next day, five injections were made betwen 8:30 a.m. and 9:30 p.m., until a total of 15 cc. had been given. By the second day following the exercise he was eating and appeared in good condition so that only two injections of 2 cc. each were given. On the third day in the morning, he

was found prostrate. The eyes were glassy. Rectal temperature was 36.0° C. He showed heightened irritability, a slight stimulus causing him to jerk or twitch. Two cc. of extract was given immediately through the intraperitoneal route. His breathing was very irregular and gasping at times. Within 21 minutes the breathing had become more regular, the eyes were brighter and the animal showed a little activity. One and one-half hours after the first injection a similar injection was made subcutaneously but without further improvement. Four and one-half hours after the first injection, he was again prostrate, cold, gasping; and an injection of 2 cc. intraperitoneally was without avail. He died in convulsions 17 minutes later.

Another animal (protocol 3) became prostrate a few hours after exercise. Extract failed to bring about improvement.

Protocol 3. A completely adenalectomized male guinea pig (No. 5) gained in weight on 3 cc. of extract daily. Fifty-one days after complete adrenalectomy he was exercised in the treadmill for 54 minutes (traveling 2391 feet). Three and one-half hours later he was prostrate and gasping. Three cc. of extract injected intraperitoneally failed to cause improvement. Death followed within an hour.

Realizing that it is much more difficult to give adequate amounts of cortin to kittens because they need it more frequently, we attempted to see whether one animal would respond to frequent injections after she had reached a serious condition. It seemed, however, that it was impossible to do more than bring about slight improvement, in the late stages in this animal, regardless of the amount of extract and frequency of injections (protocol 4).

Protocol 4. A female kitten (TQ) had the adrenals removed in two stages 11 days apart. The animal lost 60 grams between operations. The original weight was 1450 grams. Two doses of 4 cc. each were injected in the first 24 hours. On the second day she was unsteady on her legs and had slight convulsions. Therefore, 22 cc. of cortin was administered in six doses distributed over the 24 hours. On the third day the animal ate for the first time and appeared normal. She was given 14 cc. in four doses. On the fourth day this dosage was continued but on the fifth day was reduced to 9 cc. in three doses. On the sixth day she refused food and could not stand on her hind legs. At nine in the morning she had a slight convulsion. She was injected with a total of 13 cc. on that day, showing little improvement except that she appeared bright and interested in her surroundings. She would fall easily when attempting to walk because of disorientation. The legs were stiff and she moved jerkily. On the seventh day only 5 cc. was injected and that was at 8:15 in the morning. The kitten was very weak. The pupils were widely dilated. She was lying prostrate. On the eighth day the injections and condition were as follows:

8:15 a.m., 3 cc. Condition same as previous day.
11:30 a.m., 5 cc. No change.
2 p.m., 5 cc. Pupils now respond to light. The animal appeared alert but could not stand.
3 p.m. Convulsions lasting about 1½ hours, followed by prostration.
5:45 p.m. She was sitting up.
11:30 p.m., 5 cc. Appeared no worse.
2:40 p.m. on the next day she was prostrate; pupils were widely dilated. She was apparently moribund. Five cc. intraperitoneally was without effect, death occurring in 30 minutes.

Adult cats likewise failed to respond if allowed to go too far (protocol 5).

Protocol 5. A male cat 3810 gm. whose adrenals had been removed in two stages two weeks apart, had lost 380 gm. between operations. He was injected two or three times a day for the first few days, being given from three to five cc. at each injection. At first apathetic but strong, he began to show improvement and started to eat 8 days after the second operation. His appetite was

very poor, however. He finally ate as much as 45 gm. on the thirteenth day and 90 gm. on the fourteenth day, but refused food from that time, although he had become quite active and appeared in good condition. Sixteen days after the second adrenal operation, his hind legs began to appear weak in the morning, but they became normal within three hours after the injection. Injections were again given four to five times a day (5 cc. each time). Seventeen days after the second operation the animal had a number of slight convulsions. Frequent injections of cortin caused little improvement. On the eighteenth day, toward evening, he appeared somewhat better, but was very irritable, a slight stimulus causing clonic contractions. On the nineteenth day in the morning, at the time of injection, he had a convulsion and appeared to be about the same as the night before. Frequent injections failed to cause improvement. He died late that night. It was not a question of impotency of the extract because this same extract was used to maintain other adrenalectomized animals.

Because of their position in the animal scale we have studied the use of cortin (whole gland extract) in monkeys.

Two of our monkeys died during the night because no premonition of a serious condition had led us to continue frequent injections (protocols 6 and 7).

Protocol 6. A young male monkey (No. 5) was adrenalectomized in two stages 4 days apart. He lost 100 gm. (from 4250 gm.) between operations. Extract was administered as follows: 15 cc., first day; 10 cc. on each of the next 4 days; 8 cc. daily until the twelfth day. Appetite was reduced and 190 gm. more weight was lost. Return to 10 cc. extract daily caused improvement in behavior but the appetite was not completely restored. There seemed to be no evidence for concern; therefore, this last dosage was maintained. The food consumed was about 75 per cent of the former amount but the animal's activity was not greatly lessened. The animal was found dead 16 days after the removal of the second adrenal, 13 hours after the last injection. He had lost 365 gm. from the original weight.

Protocol 7. A young female monkey (No. 3) was adrenalectomized in two stages one month apart. She lost 170 gm. (from 3650 gm.) between operations. Extract was administered as follows: 15 cc. daily for the first week; 10 cc. daily for 5 days and then 8 cc. daily. Within 3 days after the second reduction her appetite had diminished so that the food consumption had been reduced about 40 per cent. Increase of the extract to 10 cc. daily produced little change. On the fourth day after this increase she appeared lackadaisical, so that an extra injection of 5 cc. was administered about noon. Her appetite was improved on that day. Twelve cc. was finally given as the daily dose.

It has always been necessary to catch and hold the monkeys in order to make the injections. This, of course, increases the demand for cortin, because of the greater stress under which the animal was placed. Occasionally a monkey will escape from its cage when preparations for injections are made; he is then apt to race about the room before he is caught; this tires him considerably. The monkey under discussion escaped from her cage at the time of preparing for the evening injection, 26 days after the removal of the second adrenal. After being returned to the cage following the injection, she was so tired that she was almost on the point of collapse. In a few minutes the breathing became very difficult and she would not respond if touched; however, within 45 minutes she was sitting up, but still weak, so that another injection of 10 cc. was given intraperitoneally. In 3 hours she appeared much better and ate half of a banana. The next day she appeared listless, ate about half of her usual food; for that reason she was injected with 10, 5 and 10 cc., respectively, at 9:30 a.m., 12:30 p.m. and 8:00 p.m.; this being two and one-half times her usual dosage. We thought that the animal would be carried through the night satisfactorily, but the next morning she was dead. She had lost 580 gm. since the second operation.

We believe that the stress to which this animal was subjected following escape from the cage was a large factor in bringing about her sudden death. She had shown evidence of a chronic cortical insufficiency for some time; this, however, seemed to be of minor degree.

These animals illustrate what we have occasionally found that an adrenalectomized animal will die without adequate premonitory signs.

Two monkeys failed to recover from frequent doses of cortin apparently because they had gone too far (protocols 8 and 9).

Protocol 8. A young male monkey (No. 4) adrenalectomized in two stages 6 days apart lost 170 gm. in weight (from 3370 gm.).

The second operation was performed at 12:15 p.m. Seven and one-half cc. of extract was injected immediately. At 8 p.m. the dose was repeated. The next morning he appeared ill as he was supporting himself against his water can. Within five minutes he was lying prone, whereupon he was injected intraperitoneally with 5 cc. of extract. He had bloody diarrhea and his respirations were 28 per minute.

One hour later 5 cc. was injected subcutaneously. Injections were repeated at intervals of one to three hours until 10:45 that night, a total of 32 cc. being administered during the day. Two-thirds of this was given intraperitoneally. By 1:45 p.m. the rectal temperature had fallen to 35.0° C. At 10:45 p.m. he began to show strength, although he could not sit up; he could hold onto the cage with considerable force when injected. Seven hours later the animal appeared much better but could not sit up. The rectal temperature had risen to 37.2° C. and the respirations were 45 per minute. During the second day after the operation frequent injections were made until a total of 30 cc. of extract had been administered. The animal showed no further improvement; he had slight convulsions in the middle of the afternoon, and occasionally jerked his muscles.

During the third day after the operation further improvement was shown. The pupils seemed smaller, and the animal appeared to notice his surroundings; he tried to get up, but was too weak, could not even hold his head up, though he did move it about. During this day he was given 28 cc. in five injections. No injections were made until 6:40 a.m. the fourth day after the operation, when 10 cc. was administered intraperitoneally; this was 10.5 hours after the last previous injection. The animal was much worse, being very weak; the rectal temperature was 35.0° C.; feces had been evacuated, but blood was absent. Respiration was very shallow, with occasional deep movements. He would open his eyes occasionally, but otherwise showed no response. An hour after this injection respirations became deeper and the animal frequently attempted to bestir himself. Two hours after the injection there were occasional jerks; three and one-half hours after the injection breathing had almost stopped, was very irregular, and came in gasps. Extract was injected intraperitoneally (5 cc.) but the animal showed slight reaction to the injection, dying 13 minutes later. Dr. Sanes found a small piece of adrenal tissue about 0.2 cm. in diameter on the right side.

Protocol 9. A young male monkey (No. 6) adrenalectomized in two stages 4 days apart lost 35 gm. in weight (from 3025 gm.). Fifteen cc. of extract was injected during the first day; 10 cc. daily for the next 4 days; 8 cc. daily for 6 days. On the twelfth day appetite was diminished. Resumption of 10 cc. daily caused prompt improvement but after 4 days all food was refused. On the morning following at 10:40 a.m. the animal was prostrate and in convulsions. He was immediately injected intraperitoneally with 10 cc. of extract. Within 30 minutes the animal was standing. He soon became weak again and for the rest of the day alternated between prostration and weakly sitting following the frequent injections. By evening, however, greatly improved, he was strong and active. During this day and the following night 64 cc. of extract was injected (20 cc. intraperitoneally).

For the next 6 days the animal appeared to be in good condition; his appetite was excellent. He was receiving 15 to 16 cc. of extract daily in two doses. On the seventh day (25th after second operation) he again became prostrate. During that day he was given 48 cc. of extract (20 cc. intraperitoneally) divided into five injections. Although he showed considerable improvement he did not fully recover, and was never completely normal in appearance and action thereafter. An edematous condition was noted in the region where the subcutaneous injections had been given, which gradually grew worse during the next three days, involving the hip, scrotum, and prepuce. This was undoubtedly due to toxic material in the extract. The edema lasted a week. During this period the animal was injected intraperitoneally, receiving on an average 31 cc. daily for 6 days. But in spite of this large amount of extract, the animal gradually grew weaker, and on the thirty-second day after the second operation he again had

convulsions. The convulsions ceased ten minutes after giving 10 cc. of extract. During that day and the next two days the animal slowly improved and became fairly strong and active, but he did not regain his appetite. During this period he received extract as follows: thirty-second day, 45 cc.; thirty-third day, 50 cc.; thirty-fourth day, 40 cc. On the thirty-fifth day after the second operation, the animal collapsed at noon. He never recovered, dying at midnight, although during that day he had received a total of 55 cc. of extract. At the time of his death the monkey had lost 410 gm. in the 35 days since the removal of the second adrenal.

DISCUSSION

It seems impossible to know when adrenal insufficiency becomes irreversible. Animals not only in convulsions or prostrate, but dyspneic and cold, can be returned to health. Some individuals, however, continue to go down hill and die in spite of treatment begun at a comparatively early stage. A halt in the downward course or even temporary improvement may be shown in these cases.

The irreversible state seems to develop more readily under the stress of toxins and exercise. It develops easily during the period immediately following adrenalectomy (Protocol 8). This may be due to the increased demand during healing. Abortions likewise accentuate the demand.

Recognition of this has led us to increase dosage considerably whenever an adrenalectomized animal is required to meet a stress and especially when the slightest sign of insufficiency appears. If this is not done the stage of irreversibility may be reached. Long continued insufficiency is also dangerous because of the greater difficulty in preventing the onset of irreversibility (Protocol 7).

In experiments where the animal was in the late stage of adrenal insufficiency larger doses of extract could have been given but it seemed wiser to repeat frequently. If no improvement whatsoever was shown as in the last crisis of guinea pig No. 7 (Protocol 1) more extract was not used because death occurred too soon. In some animals if the improvement failed to progress beyond a certain point with large amounts of extract, it was considered hopeless (Protocols 4 and 5).

Repeated relapses to the point of prostration likewise seem to make recovery more difficult.

Sudden death which occurs in adrenalectomized animals without obvious cause is probably due to adrenal insufficiency.

What holds true for animals probably holds true for man in adrenal insufficiency. At least the conditions which develop appear to be quite similar. A stage may be reached in which cortin may cause little or no improvement. Death may occur with little warning. Therefore similar treatment to that required in animals is advisable in Addison's disease.

Patients suffering from this malady sometimes die under treatment with cortin because exacerbation of symptoms is not accepted as a warning that increased dosage should be speedily instituted.

It must be recognized that adrenal insufficiency can pass into an irreversible state and that this condition may develop with little warning.

SUMMARY

Adrenalectomized animals are described in which relatively large amounts of cortin failed to produce more than temporary improvement in a crisis which had developed spontaneously or as a result of exercise. Three guinea pigs, two cats and two monkeys died in spite of cortin injections. Two monkeys died during the night without premonition of a serious condition.

Adrenalectomized animals with or without cortin treatment may pass into a stage of insufficiency from which it seems impossible to bring about recovery. This stage seems to vary with different individuals and may occur with little warning. The application of these findings to Addison's disease is discussed.

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EXPERIMENTAL STUDIES ON THE HYPOPHYSIS CEREBRI
I. THE EFFECT OF SINGLE PREGNANCY IN THE ALBINO RAT

SAM I. STEIN
Department of Anatomy, University of Minnesota
MINNEAPOLIS

INTRODUCTION

The initial observation that the pituitary gland varies in size and histologic structure during pregnancy was first reported in 1899 by Comte (1), who described a hypertrophy and hyperplasia in the human hypophysis.

Other investigators, Launois and Mulon (2), Mayer (3), Alin (4), and Biedl (5), on human material, agree with the classical observations of Erdheim and Stümme (6), namely, that during pregnancy the gland increases in size. In addition, the latter maintained that while in the nullipara the chief cells or chromophobes are less abundant than the chromophilic cells, during pregnancy an increase in the number of chief cells occurs with a simultaneous change in their histologic character to such an extent that they should be spoken of as a new cell-type, the pregnancy cell (Schwangerschaftszelle). Biederman (7) decided that they are weakly basophilic. After termination of pregnancy, an involution of the pregnancy cells occurs, and they revert back, for the most part, to their old structure. This increase in the number of chief cells tends to persist. In the case of a subsequent pregnancy, the changes in the cells occur again even to a higher degree, the hypophysis of a multipara being distinguished by the relatively larger number of chief cells.

Among the investigators on lower forms we find considerable differences of opinion.

Guerrini (8), in pregnant dogs and rabbits, found increased activity in all three types of cells. Morandi (9) claimed increased chromophilia in pregnant guinea pigs. On the other hand, Nägeli (10), in the guinea pig and also the rat, and Berblinger (11), in the guinea pig, found an increase in the choromophobes or chief cells. Pende (12), in the cat, and Watrin (13), in the sheep, describe only an increase in weight of the hypophysis during pregnancy. Siguret (14) observed in rabbits an increase in the number of eosinophils and a diminution in the number of chromophobes. Kolde (15), working with guinea pigs and rabbits, and Lehman (16) and Haterius (17), on rats, describe changes similar to those found by Erdheim and Stümme (6) for the human. Schenk (18) claimed he could not make out any definite or characteristic changes in the histologic picture of the pregnant rat hypophysis, while Herring (19) reports a 24 per cent decrease in the weight of the whole gland and a great diminution of

granular acidophils. In swine Kostner (20) gets 100 per cent increase in weight of the hypophysis in later stages of pregnancy, decreased acidophilia and development of a new type of cell. Urasov (21) claims that in the mouse there is an increase in size of the organ due to enlargement of the basophils and development of a new cell of basophilic nature.

Wittek (22) and Rosta (23), in the cow, found no changes resulting from pregnancy. Atwell (24) found no strikingly significant change in the relative volume of the epithelial lobes to accompany the progress of pregnancy in the cat.

Bell (25) sums up the situation quite well: "My own observations have impressed me with the fact that considerable variations may be found during pregnancy both in animals and women. The essential change, however, in the pars anterior of all animals during pregnancy is towards greater activity and this may be represented by increased eosinophilia of the epithelial elements or chromophobia."

Besides anatomical data, many physiological data are available which indicate that the pituitary increases its activity during pregnancy. Experimentally, Smith (26), Aschheim and Zondek (27), and Smith and Engle (28) pointed out that large amounts of anterior pituitary hormone are found in the urine of pregnant women. Also clinically, Alin (4), Beidl (5), Kark (29), and Jung (30), report cases in which pregnant women have demonstrated symptoms of acromegaly and hyperpituitarism which disappeared upon delivery of the child.

The variations in the reports so far published would seem to indicate that there is need for a more systematic, quantitative investigation of this whole problem. These results on the primipara, together with work which is to follow on the multipara, may help to clarify the situation.

MATERIALS AND METHODS

The animals used in this investigation consisted of 66 female albino rats (Mus Norwegicus albinus) of standard, vigorous Wistar stock, carefully reared and kept from birth to the time of autopsy. The animals were divided into three groups, with 22 animals in each group, one animal for each day of the gestation period, which in a rat is 22 days.

One group of animals was retained as controls and each animal was killed at the same body weight of 185 gms. The test animals were impregnated at a weight of 175 gms. Impregnation was done at the above weight on the assumption that the test animals when killed would have attained an average body weight similar to the controls if pregnancy had not been induced.

The animals were killed by placing them in a closed jar containing chloroform. The gross weight, body length and tail length were recorded. Special care was given to the removal of the hypophysis during autopsy procedure to avoid excess drying or mechanical injury.

TABLE I

No. of rat	Oestrus	Age of rat days	Body wt. gm.	Body Length cm.	wt. whole gland mgm.	Pars Anterior wt.	Pars Anterior %	Pars Posterior wt.	Pars Posterior %	Pars Intermedia wt.	Pars Intermedia %	Chromophobes No.	Chromophobes %	Acidophils No.	Acidophils %	Basophils No.	Basophils %	No.of cells counted Total	No.of cells counted Av.per field
A. Absolute and Relative Weights of Lobes of Hypophysis of Control Animals												**D. Differential Cell Count in Hypophysis of Control Animals**							
30-360	II	120	183	19.8	11.6	10.33	89.1	0.69	7.6	0.36	3.3	5153	72.9	1762	24.9	154	2.2	7069	96
30-344	II	195	182	20.3	11.2	9.83	87.7	0.92	8.2	0.45	4.1	7643	75.3	2207	21.8	292	2.9	10142	131
30-331	II	93	192	20.2	12.2	10.90	89.3	0.75	6.2	0.55	4.5	5643	74.0	1758	23.1	220	2.9	7621	107
30-366	III	90	186	20.0	10.6	9.16	86.4	0.79	7.5	0.65	6.1	6130	73.4	1952	23.4	267	3.2	8349	117
30-301	III	101	179	19.9	14.4	12.83	89.1	0.98	6.8	0.59	4.1	7431	86.0	1001	11.6	209	2.4	8641	118
31-012	IV	110	183	20.1	10.0	8.58	85.6	0.97	9.7	0.45	4.5	6164	76.2	1674	20.7	255	3.1	8093	115
30-367	IV	128	183	20.5	12.4	10.99	88.6	0.88	7.1	0.53	4.3	6624	75.5	1719	19.6	430	4.9	8773	120
30-355	IV	122	185	19.9	10.4	9.03	86.8	0.87	8.4	0.50	4.8	5600	72.5	1684	21.8	436	5.7	7722	105
30-346	IV	153	183	19.9	9.7	8.28	85.4	0.81	8.3	0.61	6.3	5914	76.2	1430	18.4	416	5.4	7760	110
30-324	IV	96	188	19.8	9.6	8.38	87.3	0.75	7.8	0.47	4.9	6779	77.9	1645	18.9	283	3.2	8707	111
30-309	V	93	193	20.4	10.4	8.98	86.4	0.85	8.2	0.57	5.4	6296	80.2	1368	17.4	191	2.4	7855	109
30-294	V	94	192	19.5	9.6	8.56	89.2	0.59	6.1	0.45	4.7	4951	62.9	2608	33.2	306	3.9	7865	112
30-311	V	94	187	19.9	10.9	9.65	88.6	0.74	6.8	0.51	4.6	5741	75.5	1651	21.7	214	2.8	7606	106
30-317	V	94	189	19.9	9.8	8.43	86.0	0.84	8.5	0.53	5.5	4831	76.7	1292	20.5	174	2.8	6297	88
30-325	V	95	192	19.7	11.4	9.97	87.5	0.86	7.5	0.57	5.0	4323	67.2	1826	28.4	280	4.4	6431	98
30-328	V	96	189	20.4	11.2	9.98	89.1	0.74	6.6	0.48	4.3	5374	80.0	1152	17.1	193	2.9	6719	92
30-310	V	100	181	19.2	9.8	8.31	84.8	0.88	9.0	0.61	6.2	4456	65.2	2134	31.2	249	3.6	6839	102
30-299	V	101	182	20.1	9.2	7.94	86.3	0.79	8.6	0.47	5.1	6759	79.7	1522	17.9	206	2.4	8487	117
30-342	V	141	182	20.2	8.4	7.41	88.2	0.62	7.4	0.37	4.4	7300	72.0	2360	23.5	462	4.5	10142	137
30-353	V	69	183	19.8	9.0	7.65	87.2	0.68	7.6	0.47	5.2	6671	74.0	2044	22.7	300	3.3	9015	115
31-021	V	109	182	20.3	8.4	7.16	85.3	0.70	8.3	0.54	6.4	6581	71.3	2365	25.9	283	2.8	9227	123
30-370	-	78	185	18.5	10.6	9.36	88.3	0.79	7.5	0.45	4.2	5985	66.9	2780	31.0	186	2.1	8951	119
Average		108	184	19.9	10.5	9.18	87.4	0.80	7.7	0.51	4.9	6015	74.1	1817	22.5	273	3.4	8105	111
B. Absolute and Relative Weights of Lobes of Hypophysis of Series I Test Animals												**E. Differential Cell Count in Hypophysis of Series I Test Animals**							
	Days pregnant																		
31-020	1	97	173	19.3	9.8	8.48	86.6	0.69	7.0	0.63	6.4	5692	71.1	2076	25.9	238	3.0	8006	109
31-014	2	106	179	20.2	11.8	10.35	87.7	0.89	7.5	0.56	4.8	6259	70.1	2429	27.2	241	2.7	8929	120
30-368	3	128	174	19.9	11.0	9.72	88.4	0.83	7.6	0.45	4.0	6207	74.4	1896	22.7	237	2.9	8340	122
30-364	4	116	184	20.2	11.8	10.31	87.3	0.99	8.4	0.50	4.3	5645	70.0	2029	25.2	389	4.8	8063	103
30-359	5	126	184	20.0	11.0	9.53	86.7	0.95	8.6	0.52	4.7	5919	70.0	2357	26.7	282	3.3	8458	120
30-298	6	106	189	19.7	10.4	8.97	86.2	0.86	8.5	0.54	5.3	6359	77.2	1663	20.2	216	2.6	8238	106
30-339	7	101	199	20.6	13.0	11.81	90.8	0.66	5.1	0.53	4.1	6000	77.3	1442	18.6	315	4.1	7757	99
30-363	8	123	187	19.7	10.8	9.23	85.4	0.92	8.5	0.45	4.1	5009	74.9	1298	19.4	378	5.7	6685	92
30-318	9	104	195	19.9	10.8	9.39	86.9	0.85	7.9	0.56	5.2	5774	71.9	1837	22.9	420	5.2	8031	104
30-343	10	163	190	20.1	11.6	10.26	88.5	0.88	7.6	0.46	3.9	6348	71.5	2099	23.7	427	4.8	8874	121
30-321	11	115	201	20.9	9.1	7.99	87.8	0.78	8.6	0.33	3.6	7323	72.4	2443	24.2	349	3.4	10115	133
30-323	12	115	190	20.4	8.9	7.54	84.7	0.83	9.4	0.50	5.6	5987	74.3	1801	22.4	265	3.3	8053	120
30-345	13	117	194	20.0	7.0	5.86	84.0	0.74	10.5	0.38	5.5	6701	71.5	2353	25.1	319	3.4	9373	137
30-313	14	103	216	20.1	10.6	9.41	88.7	0.76	7.2	0.43	4.1	5618	74.6	1645	21.8	269	3.6	7532	99
30-354	15	117	214	20.3	8.6	7.20	83.7	0.92	10.7	0.48	5.6	6116	67.4	2444	26.9	516	5.7	9076	127
30-308	16	112	222	20.9	9.6	8.26	86.1	0.80	9.1	0.46	4.8	7251	78.4	1750	18.9	247	2.7	9248	120
30-352	17	115	206	19.9	10.0	8.62	86.2	1.00	10.0	0.38	3.8	5183	70.7	1794	24.5	351	4.8	7328	107
30-369	18	103	220	20.5	10.2	8.55	83.8	1.05	10.3	0.60	5.9	5693	69.3	2161	26.3	358	4.4	8212	122
30-293	19	96	241	19.9	8.0	7.06	88.2	0.59	7.3	0.35	4.5	4413	67.0	1893	28.7	281	4.3	6587	109
30-312	20	96	238	20.1	8.3	7.07	85.2	0.80	9.6	0.43	5.2	6612	81.4	1273	15.7	236	2.9	8121	112
30-300	21	131	226	20.3	8.6	7.50	87.2	0.74	8.6	0.36	4.2	5097	74.7	1412	20.7	318	4.6	6827	106
30-330	22	119	202	21.0	11.2	10.07	89.9	0.65	5.8	0.48	4.3	5938	77.6	1354	17.7	361	4.7	7653	104
Average		109	201	20.2	10.1	8.78	86.8	0.83	8.4	0.47	4.7	5961	73.1	1879	22.9	318	3.9	8114	113
C. Absolute and Relative Weights of Lobes of Hypophysis of Series II Test Animals												**F. Differential Cell Count in Hypophysis of Series II Test Animals**							
31-232	1	117	176	20.2	10.8	9.46	87.6	0.85	7.9	0.49	4.5	7120	79.7	1757	19.7	59	0.6	8936	122
31-163	2	199	179	20.3	10.0	8.76	87.6	0.79	7.9	0.45	4.5	5887	75.7	1681	21.6	207	2.7	7775	111
31-231	3	143	182	19.7	8.4	7.34	87.4	0.67	7.9	0.39	4.7	5476	74.9	1568	21.4	271	3.7	7315	112
31-178	4	170	186	19.9	10.8	9.78	90.6	0.62	5.8	0.37	3.5	5963	75.1	1674	21.1	299	3.8	7936	115
31-233	5	142	180	19.8	10.6	9.41	88.8	0.78	7.4	0.41	3.8	6031	74.4	1715	21.2	361	4.4	8107	114
31-133	6	175	194	19.9	14.6	12.99	89.0	0.96	6.6	0.65	4.4	7978	81.8	1455	14.9	324	3.3	9757	126
31-131	7	177	186	20.4	11.4	10.06	88.2	0.93	8.2	0.41	3.6	7362	84.5	1170	13.4	179	2.1	8711	119
31-181	8	170	188	19.9	9.8	8.58	87.6	0.70	7.2	0.52	5.2	5708	68.8	2248	27.1	341	4.1	8297	113
31-180	9	152	179	19.8	10.4	9.26	89.0	0.69	6.6	0.45	4.4	6783	80.5	1298	15.4	350	4.1	8431	112
31-051	10	230	205	19.8	11.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-
31-132	11	159	188	19.8	9.2	7.90	85.9	0.89	9.6	0.41	4.5	7884	85.6	1036	11.2	294	3.2	9214	126
31-129	12	170	194	20.2	10.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-
31-038	13	239	198	19.8	10.0	8.41	84.1	0.94	9.4	0.65	6.5	7175	81.1	1272	14.4	397	4.5	8844	126
31-123	14	170	189	20.1	11.0	9.11	82.8	1.29	11.8	0.60	5.4	7906	79.5	1583	15.9	456	4.6	9945	134
31-137	15	161	195	20.7	9.6	8.30	86.4	0.79	8.2	0.51	5.4	7588	82.0	1353	14.6	313	3.4	9254	126
31-127	16	160	204	20.3	6.8	5.75	84.5	0.66	9.8	0.39	5.7	5871	71.3	1957	23.8	403	4.9	8231	112
31-125	17	104	212	20.3	8.4	7.17	85.3	0.78	9.2	0.45	5.5	7129	78.1	1601	17.5	404	4.4	9134	125
31-052	18	130	221	20.2	10.4	8.97	86.2	0.88	8.4	0.45	4.4	6960	77.5	1699	18.9	319	3.6	8978	118
31-055	19	127	251	20.8	11.4	10.04	88.1	0.87	7.7	0.46	4.0	7343	81.2	1450	16.0	255	2.8	9048	125
31-054	20	126	214	20.0	10.6	9.27	87.5	0.89	8.4	0.44	4.1	7061	79.7	1571	17.7	227	2.6	8879	130
31-056	21	122	246	20.6	11.2	9.86	88.1	0.83	7.4	0.46	4.1	6504	70.9	2288	25.0	376	4.1	9168	123
31-041	22	118	211	20.8	10.0	8.6	86.4	0.87	8.7	0.49	4.9	6885	83.8	1119	13.6	210	2.6	8214	111
Average		153	198	20.2	10.3	8.9	87.1	0.83	8.2	0.47	4.7	6831	78.3	1575	18.2	302	3.5	7916	120

The material was preserved in saturated mercuric chloride to which was added 10 per cent formalin.

The paraffin sections were cut at 5 micra. A volumetric study of the three lobes and a differential cell count and histologic survey of the anterior lobe were made. For the volumetric procedure the method followed was that of Hammar (31). Every tenth section was mounted and stained with hematoxylin and eosin. The image of each section, magnified 33 diameters, was outlined on paper of uniform thickness, cut out, and the paper weighed on a chemical balance, from which the percentage of each lobe was calculated.

For the histologic study and differential cell count about five sections at well distributed intervals were taken, stained with a modified Mallory's triple connective tissue stain so that the nuclei stood out clearly, and made the cell count more reliable. The modification consists in staining a fraction of a minute in ordinary Harris' haematoxylin before using acid fuchsin, as done by Rasmussen (32).

Three types of cells were distinguished similar to most classifications, namely, easinophils (acidophils, oxyphils, alpha cells), basophils (cyanophils, beta cells) and neutrophils (chromophobes, chief cells, reserve cells, undifferentiated cells). About 8,000 cells were counted in each gland.

No study of pars tuberalis was made for it had been left attached to the brain during autopsy procedure.

RESULTS

A. Weight of the Whole Hypophysis

As shown in Tables IA and IB, the control group and Series I tests have an identical average age, while Series II tests (Table IC) are on an average 45 days older. This age difference may explain certain significant differences in the results obtained between the two groups.

Table II shows that there is no significant difference in the body lengths of the three groups of animals.

TABLE II

STATISTICAL CONSTANTS FOR BODY LENGTH

Animals	M ± S. E. m	Diff. ± S. E. Diff.	Diff. S. E. Diff.	P	C. V.
Control.....	19.92 ± 0.099	.....	....	..	2.3
I Series.....	20.18 ± 0.090	+0.25 ± 0.134	1.89	6	2.1
II Series.....	20.16 ± 0.127	+0.24 ± 0.161	1.47	14	2.8

No significant difference can be pointed out between the average weight of the whole hypophysis of the control and either of the test groups (Table III), showing that one pregnancy had not altered the weight of the whole hypophysis.

TABLE III

STATISTICAL CONSTANTS FOR WEIGHT OF WHOLE HYPOPHYSIS

Animals	M ± S. E. m	Diff ± S. E. Diff.	Diff. S. E. Diff.	P	C. V.
Control.....	10.49 ± 0.292	.....	....	..	13.0
I Series.....	10.10 ± 0.306	—0.40 ± 0.423	0.94	35	14.2
II Series.....	10.27 ± 0.334	—0.22 ± 0.443	0.50	62	14.5

M—Mean. P—Number of chances in 100 that the differences may be due to errors in random sampling. C. V.—Coefficient of Variation. S. E.—Standard Error (coming into use to replace probable error).

Since S. E. $= \frac{\text{Probable Error}}{.6745} = \frac{\text{Standard Deviation}}{\sqrt{n \text{ or } n-1}}$ (n = number of cases), the factor .6745 is dispensed with, and the ratio of the difference between means and the standard error of the differences needs only to be 2 to indicate that there are 95 chances out of 100 that the difference is real and not merely due to random sampling, which is generally considered significant. For the value of statistical methods in this type of work see Dunn (33).

Inspection of Tables IB and IC and Graph I (Fig. 1) reveals no trend of increase in the weight of the gland with the duration of pregnancy.

B. Absolute and Relative Volume of the Lobes

The results of this part of the experiment are summed up in Tables 1A, IB, IC and IV. In these and some other tables, the percentages do not total 100 in all cases because colloid is not included.

TABLE IV

STATISTICAL CONSTANTS FOR ABSOLUTE AND RELATIVE WEIGHTS OF THE INDIVIDUAL LOBES

Animals	M ± S. E. m	Diff. ± S. E. Diff.	Diff. S. E. Diff.	P	C. V.	M ± S. E. m	Diff. ± S. E. Diff.	Diff. S. E. Diff.	P
	Pars Anterior (Absolute Weight)					Pars Anterior (Relative Weight)			
Control...	9.18 ± 0.277	.....	....	..	14.2	87.38 ± 0.30	.....	....	..
I Series..	8.78 ± 0.293	—0.39 ± 0.403	0.95	35	15.6	86.82 ± 0.40	—0.56 ± 0.50	1.11	26
II Series..	8.95 ± 0.313	—0.22 ± 0.418	0.53	59	15.6	87.06 ± 0.41	—0.32 ± 0.51	0.63	52
	Pars Intermedia (Absolute Weight)					Pars Intermedia (Realtive Weight)			
Control...	0.509 ± 0.015	.....	....	..	13.8	4.91 ± 0.17	.....	....	..
I Series..	0.473 ± 0.017	—0.036 ± 0.023	1.58	11	16.7	4.72 ± 0.23	—0.19 ± 0.23	0.79	42
II Series..	0.474 ± 0.017	—0.035 ± 0.023	1.53	12	15.7	4.66 ± 0.17	—0.25 ± 0.24	1.02	31
	Pars Posterior (Absolute Weight)					Pars Posterior (Relative Weight)			
Control...	0.803 ± 0.022	.....	....	..	12.6	7.71 ± 0.19	.....	....	..
I Series..	0.831 ± 0.025	+0.027 ± 0.033	0.83	40	14.0	8.36 ± 0.30	+0.64 ± 0.35	1.81	7
II Series..	0.833 ± 0.032	+0.030 ± 0.038	0.77	44	16.9	8.19 ± 0.29	+0.48 ± 0.35	1.36	18

On the whole, we find no significant differences (Table IV) between the absolute and calculated relative weights of the various lobes in any of the three groups. Thus we find that not only the average whole weight of the glands remained the same, which is contrary to the general opinion for pregnancy, but also fail to show any significant difference in the relative weight or size of any of the lobes. The whole weight of the gland

might have remained the same and the anterior lobe increased at the expense of the other two, but this does not seem to be the case here, as is also shown in Graphs II, III and IV (Figs. 2, 3, 4).

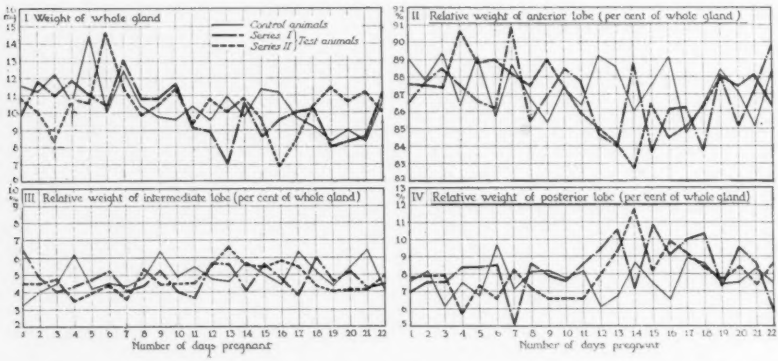
I Weight of whole gland
Control animals
Series I / Test animals
Series II
II Relative weight of anterior lobe (per cent of whole gland)
III Relative weight of intermediate lobe (per cent of whole gland)
IV Relative weight of posterior lobe (per cent of whole gland)
Number of days pregnant
Number of days pregnant

Figure 1. Graph of the absolute weight of the whole hypophysis (without stalk and pars tuberalis) of all three series according to days of pregnancy. Shows no trend of increase or decrease of the whole gland with the duration of pregnancy.

Figure 2, 3, 4. Graphs of the weight of the three principal lobes as percentage of the whole gland of all three series according to days of pregnancy. No trend of increase or decrease in the relative size of any of the lobes is evident.

C. Relative Number of Different Types of Cells in the Anterior Lobe

Tables ID, IE, IF and V show the results obtained in the differential cell count.

The difference of age, body length and weight of whole gland must again be considered. The latter two factors have been ruled out, for no

TABLE V

STATISTICAL CONSTANTS OF PERCENTAGES FOR DIFFERENTIAL COUNT OF CELLS IN ANTERIOR LOBE

Animals	M ± S. E. m	Diff. ± S. E. Diff.	Diff. S. E. Diff.	P
	Chromophobes			
Control	74.16±1.11	.....	....	..
I Series	73.08± .78	−1.07±1.36	.79	42
II Series	78.30±1.02	+4.15±1.56	2.7	.7
	Acidophils			
Control	22.49±1.07	.....	....	..
I Series	22.97± .73	+ .48±1.30	.38	19
II Series	18.23± .94	−4.26±1.42	2.9	.3
	Basophils			
Control	3.36± .21	.....	....	..
I Series	3.95± .16	+ .59± .27	2.2	.3
II Series	3.47± .23	− .11± .31	.36	70

significant differences were obtained. The average age difference of 45 days between Series II tests and that of the controls and Series I tests is very significant, since the animals have not attained full maturity.

From a study of Table V one can see that there is no significant difference between the average percentage of the various types of cells in the anterior lobes of the control group and Series I tests.

There is, however, a slight significant difference between the average percentage of the chromophobes and acidophils of the control group and Series II tests. There are about 4 per cent more chromophobes in Series II tests than in the controls, with a corresponding increase of about 4 per cent of acidophils in the controls, while the percentage of basophils remains the same. This is not a pronounced difference, but is statistically significant.

The results obtained from controls and Series I tests are much more reliable in view of the fact that these animals were litter mates and of identical ages. The difference between Series I tests and Series II tests is probably not due to pregnancy for, other than this age difference, the two series were treated exactly alike.

Apparently the cells in Series II tests were considerably smaller than in the other two groups. This is shown by the significant difference which exists between the average number of cells counted per field in the control and Series I test groups as compared with that of Series II tests. This assumes that the relative proportion of parenchyma to sinusoids in the three sets of glands was equal, which appears to be the case, although no quantitative work was done on this phase. Table VI shows an average

TABLE VI

NUMBER OF CELLS PER FIELD IN ANTERIOR LOBE

Animals	M ± S. E. m	Diff. ± S. E. Diff.	Diff. S. E. Diff.	P
Control	111±2.91	.....	....	...
I Series	113±2.95	+2±4.14	.48	55
II Series	120±1.56	+9±3.30	2.70	.7

difference of about 7 cells per field, which is quite significant. From 70 to 80 fields of equal size were counted in each gland and the average number of cells per field is based on about 1500 fields in each group of animals.

Tables IE and IF and Graphs V and VI (Figs. 5, 6) indicate that there is no trend of increase in the relative percentages of any of the three types of cells with the duration of pregnancy, considering the rather wide range of individual variability which perhaps is to be expected from data of this sort.

It was hoped that this study would determine if there were any changes in cell count in the glands of the control group during the various stages of the oestrus cycle as has been claimed by Reese (34), Wolfe (35), and Charriper and Haterius (36). Unfortunately, however, 17 of the 22

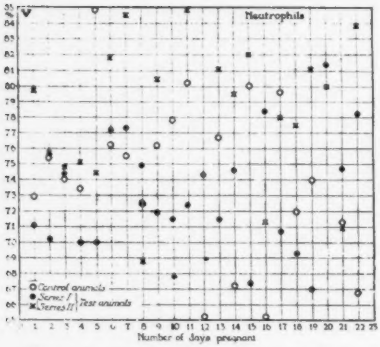

Figure 5. Field graph of the percentage of neutrophilic (chromophobe) cells of the anterior lobe of all three series according to days of pregnancy, showing considerable individual variability.

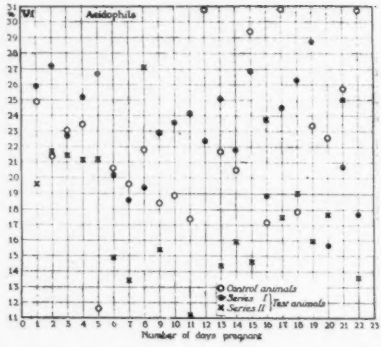

Figure 6. Field graph of the percentage of acidophils (alpha cells) of the anterior lobe of all three series according to days of pregnancy, showing much individual variability.

animals at the time of autopsy fell into the metestrus (postestrus) and anestrus (diestrus) stages. Only 4 of the glands were in the oestrus and late oestrus stages, so that the apparent differences are not necessarily real but may be merely errors due to small samples. The actual figures for stage II (3 animals), were 74 per cent chromophobes and 23 per cent acidophils; for stage III (2 animals), 79.6 per cent chromophobes and 17.4 per cent acidophils; for stage IV (5 animals), 75.6 per cent chromophobes and 19.8 per cent acidophils; and for stage V (12 animals), 72.5 per cent chromophobes and 24.2 per cent acidophils.

D. Histology

The histologic structure of the three groups of glands can be considered together for it appears as if a similar morphology exists in all. The tissue was well fixed and stained very distinctly with Mallory's triple connective tissue stain. The three types of cells—chromophobes, acidophils and basophils, can easily be differentiated from one another.

(a) *Chromophobes.* These remain colorless for the most part. However, if the gland was slightly overstained with acid fuchsin (Mallory No. 1) the chromophobes took on a pale pinkish tinge, or if overstained with aniline blue (Mallory No. 2), they took on a bluish grey tinge. However, in no way could one confuse the chromophobes with either one of the two cell types except in the area where pars anterior joined pars intermedia. In this region, on the pars anterior side I found cells larger than the chromophobes, and staining a pale blue, but smaller than the basophils, and never staining as darkly. In all respects these cells morphologically were like those found in pars intermedia. However, they were counted in with the basophils which they resembled much more than the chromophobes.

In a few instances some of the chromophobes showed orange or reddish granules in the cytoplasm. These may have been secretory granules com-

parable to those in the acidophils, but in no case were there enough granules present to change the general hue of the cell, and yet some might call them intermediate stages between acidophils and chromophobes. Apparently these granules are some organoid that stains with one of the dyes of this mixture.

As seen in the paragraph under "cell counts," the number of chromophobes varied considerably in the individual glands of the three groups. Likewise the distribution of the cells in the glands was very irregular; only a few glands showed two large definite groups of chromophobes on either side of the midline.

The size and shape of the chromophobes varied in the individual glands and with the position in the gland. In some of the glands they were quite consistently small, with little cytoplasm, if any, and with irregular cell boundaries. In some instances they were generally much larger, and the cytoplasm was definitely visible and the cell outlines more distinct. In most glands there was considerable variation in the size and shape of the cells, usually a mixture of the large and small, with the latter predominating in the periphery of the gland.

The nuclear pattern of the chromophobes varies with the size of the cell. The small cells have small, dark nuclei with a considerable amount of chromatin. Many of these cells show pycnotic nuclei. The larger cells have large, light nuclei with relatively less chromatin. Very few signs of mitosis were noted in any of these cells.

Since most authors have described the so-called "pregnancy cell" to be a large chromophobe [verified by Lehman (16) for the rat], I sought to find something similar in the glands of the pregnant animals. However, I could find no definite type of cell in the pregnant groups either from the standpoint of number, size, shape, nuclear pattern, staining or distribution in the gland, which was distinctly different from any type in the control group.

(b) The *acidophils* take on a strikingly brilliant red color which makes it rather easy to differentiate this cell from the chromophobes. The nuclear pattern of the acidophils helps somewhat to distinguish it. The nucleus stains more darkly; the chromatin is slightly clumped and a dark, fairly heavy nuclear membrane is present. They also varied considerably in size in the individual glands, sometimes consistently small and sometimes distinctly larger than usual.

There was no very definite distribution of these cells in the gland except that many of them were found along the blood sinuses.

A number of the cells showed pycnotic nuclei with dark, homogeneous cytoplasm which is in agreement with Schenk (18) who claims that these are degenerating forms. I could not find in the pregnant groups a type of acidophil which differed from any type in the control group, such as Schenk (18) designates "pregnancy cell." He describes this cell as an eosinophil which stains lighter than the normal eosinophil and has fewer

and smaller granules and an indented nucleus which contains considerably more chromatin. Schenk claimed that a cell of the latter description is present in the pregnant rat hypophysis and is an eosinophil, but which was being confused by most authors as a chromophobe and called a "pregnancy cell." I could not find cells of this description.

(c) *Basophils.* The basophils form a relatively small percentage of the total number of cells. They stain a very distinct dark blue and are easily differentiated except, as has been mentioned, at the point of junction of pars anterior with pars intermedia.

The basophils are distinctly larger than either of the other two cell types. Their nuclei are relatively small, with considerable chromatin. The nuclei sometimes stain red.

A prominent structure known as the macula was easily seen in most of the cells. This structure is located near the nucleus and is supposed to be associated with the Golgi apparatus.

The basophils were often quite limited in their distribution, being largely confined to the region adjacent to the residual lumen in many cases.

SUMMARY

1. The average weight of the whole hypophysis of two groups of pregnant white rats (22 animals in each group, one for each day of the gestation period, all primipara) shows no significant difference from the average whole weight of the hypophysis of a control non-pregnant group, consisting of 22 animals from the same colony (Table III).

2. No significant differences were found in the absolute or relative volume of the lobes between the two groups of pregnant animals if compared with each other or if compared with the control group (Table IV).

3. A differential count of the cells in the anterior lobe (based on counting about 8,000 cells in each hypophysis, Table V) showed no significant difference between Series I tests and the controls. The average percentages for Series I tests are, roughly, 73 per cent chromophobes, 23 per cent acidophils and 4 per cent basophils. For the control group the corresponding figures are 74 per cent chromophobes, 22.5 per cent acidophils and 3.4 per cent basophils.

A slight significant difference, however, was found in the cell counts between the above two groups and Series II tests. The figures for the latter are 78 per cent chromophobes, 18 per cent acidophils and 3.5 per cent basophils.

4. The cells in Series II tests were apparently smaller in size than the other two groups as indicated by the fact that this group had 120 cells per field, while the control group had only 111 and Series I tests, 113.

5. From the standpoint of number, size, shape, nuclear pattern, staining reaction or distribution in the gland, no definite type of cell could be found in the pregnant groups that was different from any type in the

control group. No sign of any so-called "pregnancy cell" could be identified.

6. Slight changes in the cell counts were noticed with the various stages of the oestrus cycle; but not enough animals were represented in some of the stages to warrant a definite statement.

7. The similarity of the hypophyses in the three groups may be due to the fact that this is only the first pregnancy for the test animals. However, one would expect that if pregnancy produces such marked change in the hypophysis as is frequently assumed from its increased physiological activity during pregnancy, it would be reflected in the size and structure of this organ even in primiparae. This does not seem to be the case in this study.

I want to take this opportunity to thank my adviser, Dr. A. T. Rasmussen, and Dr. C. M. Jackson, Director of the Department of Anatomy, for the valuable information they supplied during the course of the work, and for providing the material which made this study possible.

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Book Reviews

THE LIFE LINE OF THE THYROID GLAND. A CONTRIBUTION TO THE STUDY OF GOITER. By Robert McCarrison and K. B. Madhava. From the Indian Research Memoirs, Memoir No. 23. Thacker, Spink & Co., Ltd., Calcutta. Pp. 378. March, 1932.

This work is intended to check up on the earlier work of 1927 by the senior author and to carry this forward as far as present laboratory means permit. In the exercise of its normal function the thyroid requires some latitude both as to fluctuation in size and in histological appearance. It is an organ whose size may vary from year to year, from season to season, or it may be, from day to day, in accordance with the needs of the tissues for its products. These needs are greater at certain seasons than at others, at certain stages of bodily development and at certain physiological periods such as puberty and pregnancy. Accordingly, the gland is usually under greater stress at these times and any additional burden upon its resources may be evidenced by an increase in its size.

Before sexual maturity the thyroid gland grows more rapidly than the body as a whole; it is then that it especially requires all elements necessary for normal nutrition. It reaches its maximum weight relative to that of the body just prior to puberty; thereafter its relative size gradually diminishes in both sexes, remaining at a low level in males, but in females exhibiting secondary rises associated with reproductive activity. In size the organ thus follows a definite course throughout life. The outstanding features of this "Life Line of the Thyroid Gland" are its relatively rapid rise prior to puberty and its gradual decline as age advances after puberty. Because of its conspicuous position in the neck it is possible to observe the relatively larger size of the thyroid gland in childhood. It is shown in this memoir how the normal activities of the gland, as evidenced by its size, may be distinguished from those that are abnormal. Some reliable measurement of the gland is made in a normal universe: its weight in laboratory animals; its breadth (as suggested by P. Stocks) in the living human subject. This measurement is then considered relative to another bodily measurement—the body-weight. Both measurements should relate not to the aggregate of human beings or of animals under examination but to those falling within selected intervals of age or body-weight. A sufficient number of observations having been made for each selected interval, the mean relative size of the gland for that interval is determined by dividing the thyroid-measurement by the body-weight. Glands exceeding the normal mean by two-and-a-half times its standard deviation are of abnormal size and are to be classed as "goiter"; those not exceeding this limit are not of abnormal size, however else they may, in structure, have departed from the normal. Treated in this way many so-called "goiters" in schoolchildren may prove not to be goiters at all, but to be the normal expression of the thyroid gland's more rapid growth during childhood. Further, the curve of incidence of thyroid enlargements—as detected by this or by lesser standards—is, like the life-line of the thyroid, of characteristic shape with some exceptions; it rises rapidly to a maximum at about the age of puberty and thereafter falls steadily. The life line of the thyroid gland is profoundly affected by dietary conditions, being lowered by some and height-

ened by others. Certain dietary conditions may, besides altering its level, alter its course, causing it to persist at an abnormally high level as age advances after puberty. In certain conditions it may be heightened by insanitation.

Among goitrogenic influences mentioned in this work are an excess of fats, fatty acids and lime; deficiency of vitamin A, possibly vitamin B, vitamin C, iodine and the phosphates—the last relative to an excess of lime; and such positive goiter-producing substances as occur in cabbage, ground nuts, bran and maize, and a suspicion that these are also present in certain cereal grains.

It is frequently observed that this or that race lives under the worst possible conditions of sanitation yet are free from goiter. McCarrison's results appear to provide an explanation of their immunity; their food affords them protection against the goitrogenic action of insanitary conditions. We may visualize a locality—much as an isolated region of some mountainous country—where the soil is calcareous, the water supply loaded with lime, the iodine-content of the soil, and of foods grown upon it, relatively low, the diet of the people poor in fat-soluble vitamins and unduly rich in food materials containing positive goitrogenic agents. Add to this a condition of gross insanitation with pollution of drinking water supplies and the probability that "goiter" will arise in such a community within a given time is very high indeed. Moreover, if these conditions be peculiar to a locality "goiter" will be or will become endemic therein; and these conditions, being such as will affect residents in this locality throughout the whole course of their lives, will cause congenital manifestations of goiter—congenital goiter, cretinism, deaf-mutism, and idiocy—to make their appearance within the second or third generation. This visualization corresponds in many ways to the actual conditions prevailing in certain parts of Himalayan India, where goiter is endemic (McCarrison, 1906). It is not, however, intended to convey the impression that such a combination of circumstances will be found in every locality where goiter prevails. It is possible, for instance, that in a given locality or group of individuals iodine-deficiency may be the sole goitrogenic agent in operation; in such circumstances these observations would lead us to expect an incidence of thyroid enlargement confined mainly to early life. It may be possible to construct other sets of circumstances which might better account for the occurrence of goiter in other localities or individuals, and if these facts be not sufficient then others must be sought for. Their non-applicability to a given locality or to a given individual does not imply their inaccuracy, though it may indicate their limitations.

First and foremost among anti-goitrogenic agents are mentioned a properly balanced diet, vitamin A, questionably vitamin B, vitamin C, and iodine. The latter is a powerful antagonist to goiter formation, but its action as such is limited. It must be used with discrimination; prophylactic doses should never exceed physiological limits, and care should be taken that the diet of the person for whom iodine is prescribed is well balanced. Other anti-goitrogenic substances are sodium phosphate, which is effective against the goitrogenic action of an excess of lime in the diet, thyroxine, which is effective in preventing "cabbage-goiter," thymol, which is useful against goiter-forming substances in the intestinal tract, and manganese chloride, which is useful against the agent causing lymphadenoid goiter in rats fed on vitamin-deficient diets, and against the agent in cabbage which causes hyperplastic goiter in rabbits and rats.

This book of McCarrison and his co-worker contains a wealth of vitally important material which cannot be adequately discussed within the space of mere review. A careful study of the work will amply repay the student of the subject.

ACROMEGALY. F. R. B. Atkinson, with foreword by Sir Arthur Keith. John Bale, Sons & Danielson, Ltd., London. Pp. viii and 260. 1932.

This volume contains an extended analysis of all of the cases of acromegaly recorded in medical literature. Drawing from the original data, the author presents brief chapters on the history of the disease, its clinical appearance, pathological anatomy, symptomatology, etiology, pathogeny, diagnosis, prognosis, and treatment. This absorbs about one-third of the volume, while detailed descriptive tabulations dealing with the results of ablation, post-mortem findings, eye conditions, and a general description of cases occupies the main body of the book. A bibliography of over sixty pages completes the volume.

Patently the author has aimed at completeness in this survey and his analysis deals with the particulars of 1319 cases recorded up to the end of 1930. It is a monumental undertaking and the success which has attended it confirms alike the author's vast patience and his erudition. He has apparently felt it desirable to present varying and conflicting opinions without personal criticism of the material. While in the main this is to be regarded as a sound procedure, particularly where the content is still a matter of debate, certain matters might suitably have been critically reviewed in the light of present-day knowledge where such has received general acceptation. The failure of earlier writers to recognize the spontaneous involution of the function levels of the gland led to certain earlier misconceptions, and as a result an uncritical statistical approach falls far short of a satisfactory medium for the expression of primary trends. The effect of changing function levels on carbohydrate metabolism and on that of the energy exchange serve as excellent illustrations of this point. A second feature characterizing much of the earlier and some of the later literature which offers somewhat misleading material is the failure to recognize the influence of superimposed or coincident conditions which could and do modify both the clinical and laboratory pictures. The relative inaccuracy of the chemical methods invalidates many of the earlier objective data concerned with such topics as the mineral and nitrogen metabolism. In the chapter on Pathogeny the author reviews various theories in a somewhat more critical vein than appears in much of the other material. Emphasis is laid more strongly on tumor growth than upon deranged function, a weighting that is perhaps not entirely in harmony with the trend of the current thought. The divergent manifestations of pituitary overactivity as conditioned by the developmental stadium of the individual could be more explicitly and clearly outlined. Under the caption of Treatment the author again permits himself an occasional critical note as in the sentence, "Hypnosis has been tried without avail and what good purpose it could be expected to serve it is difficult to understand." Later in the same chapter the author comments on the varying results reported with opotherapy and at this point calls attention to the changing function levels characteristic of the condition as being the obvious explanation.

Every worker in the endocrine field owes a very real debt of gratitude to the author for assembling this vast amount of material in so condensed and available a form. Simplicity in use would have been enhanced had

the author used the same reference numbers in those tabulations containing only a fraction of the cases as appear in the compilation of the descriptions in which the total series is listed. The volume should find a place on the shelves of every investigator in the field. A genial and appreciative foreword by Sir Arthur Keith serves as a graceful introduction. The book is well and clearly printed; typographical errors are extremely rare.

ABSTRACTS

The antagonistic action of adrenal extracts in the presence of experimental epithelioma of white mice (Propriétés antitumorales d'extraits de surrénales vis-a-vis de l'épithélioma expérimental de la Souris blanche). Arloing, F., A. Morel, A. Josserand and A. Badinand, Compt. rend Soc. de biol. **109:** 101. 1932.

Extracts were made from the zona reticularis of the adrenals of rabbits. These were injected into eight white mice carrying tumors in an active state of growth. The tumors of these mice showed a much greater invasion of fibrous tissue than those of the controls.—J. C. D.

On the reciprocal action of adrenalin and pilocarpin on the blood sugar (Über den gegenseitigen Einfluss des Adrenalins und Pilocarpins auf den Blutzucker). Belàk, A. and A. Klamartsik, Ztschr. f. d. ges. exper. Med. **74:** 324. 1930.

Using the blood sugar level as an indicator for a definite vegetative function, the sympathico-tonic and blood sugar level raising action of the adrenals was studied. It was expected that the greater the sympathetic tone, the stronger the parasympathetic tone; e.g., if the parasympathetic tone is increased through pilocarpine, the action of the adrenals to cause a rise in blood sugar should be decreased. Rabbits received first a subcutaneous injection of 1 mgm. pilocarpine and 5-6 minutes later an adrenalin injection of varying concentration (0.025 to 1 mgm.). Small doses of pilocarpine were used because these have either no action on the blood sugar or produce, as a sign of increased parasympathetic tone, a hypoglycemia while larger doses cause a hyperglycemia. Blood sugar determinations were made according to the method of Hagendorn-Jensen at 5, 15, 30, 60, 90 and 120-minute intervals. An hypoglycemic dose of pilocarpine increased the adrenalin action; in other words, pilocarpine sensitized the animal to the action of adrenalin. When large doses of adrenalin were used (1 mgm.) the sensitization was shown only by the fact that the blood sugar level rose more rapidly in the pilocarpinized animals than in the normal animals. The absolute height of the blood sugar curve was not increased; in other words, the blood sugar level rose only to a certain height and if the adrenalin dose was sufficient to produce this rise, the pilocarpine was ineffective. The authors point out the various apparent discrepancies in the results obtained by them and by other observers who have studied the action of pilocarpine and adrenalin on blood sugar level. They suggest that the differences show that the action of a vegetative hormone depends largely on the condition of the nervous mechanism and that the classical theory is not sufficient to explain these actions.—A. C. Ivy.

Metabolic investigations on Addison's disease; carbohydrate metabolism (Stoffwechseluntersuchungen bei Morbus Addison. I. Über die Störungen des Kohlehydratstoffwechsels). Buresch, A., Ztschr. f. Klin. Med. **118:** 206. 1931.

Seven cases of Addison's disease are reported. Studies on the administration of sugar showed that an alimentary hypoglycemic reaction was present which was much greater than in normals. The hypoglycemia was promptly relieved by injection of adrenaline or adrenal extract (Loewe). It is concluded that Addison's patients are deficient, not in the supply of glycogen in the depots, but in the capacity to mobilize this glycogen. In one case, hypoglycemic coma was relieved promptly by the injection of 2 cc. adrenal extract. The carbohydrate metabolism of Addison's disease is discussed in relation to that of diabetes.—From Author's Summary.—J. J. Pfiffner.

The mechanisms of epinephrine action; changes in liver glycogen and blood lactic acid after injection of epinephrine and insulin. Cori, G. T., F. C. Cori and K. W. Buchwald, J. Biol. Chem. **86:** 375. 1930.

Blood sugar, blood lactic acid, and liver glycogen were determined in well fed rats at various time intervals after subcutaneous injection of epinephrine,

insulin, or both hormones. Fifteen minutes after the epinephrine injection liver glycogen was lower, after one hour it was the same, and after three hours it was higher than in control animals. Blood lactic acid which was augmented after fifteen minutes and after one hour, had returned to normal three hours after the injection, while blood sugar was still elevated at that time. On the basis of the available data it was calculated that the sugar set free in the liver in the first hour of epinephrine action amounted to only one-fourth of what a rat can use per hour. This confirms the previous contention that decreased utilization of blood sugar plays as important rôle in epinephrine hyperglycemia. Fifteen minutes after the insulin injection liver glycogen and blood sugar were unchanged, while after one hour both had diminished. When insulin and epinephrine were injected, the former prevented the decrease in liver glycogen and the increase in blood sugar regularly observed after the injection of the latter. Insulin is therefore an inhibitor of the hepatic glycogenolysis accelerated by epinephrine. Insulin has, however, very little effect on the increase in blood lactic acid resulting from the injection of epinephrine.

—Authors' Summary.

The effect of epinephrine upon the rate of contraction and upon the conduction time of peristalsis and antiperistalsis in excised ureters. Gruber, C. M., J. Pharmacol. & Exper. Therap. **39**: 449. 1930.

The rate of conduction of the contraction wave is the same whether the wave passes from kidney to bladder or vice versa. Segments taken from the ureter near the kidney and some distance from it are equally sensitive to epinephrine. Epinephrine increases the rate of conduction of both peristaltic and antiperistaltic waves in the ureter and to the same degree.

—Author's Summary.

Treatment of Addison's disease with an extract of suprarenal cortex (cortin). Hartman, F. A., G. W. Thorn, L. M. Lockie, C. W. Greene and B. D. Bowen, J. A. M. A. **98**: 788. 1932. Abst., A. M. A.

The authors report seven cases of Addison's disease treated with cortin. Three represented the severe stages of the disease and four others presented less severe aspects of the syndrome. Conclusive evidence is furnished that an extract of the suprarenal cortex prepared by the ether-alcohol method is effective in alleviating the symptoms of Addison's disease. The requirements of different patients for cortin vary over a wide range, depending no doubt on the degree of suprarenal insufficiency and also on individual variation. It has been found in animals with complete suprarenalectomy that the amount of cortin required to keep them in good condition varies considerably. This variation exists even under optimum conditions, but with infections, trauma and exercise much more cortin is needed. When the requirements are not great, the doses not only are small but need not be given frequently. As the patient's demands for cortin increase, the dosages must be stepped up both in quantity and in frequency, as is necessary, for example, in infections or in trauma. This obtains in animals and seems to be true in man. The daily total requirements both in man and in animals seem to be less if the dosage is frequent.

Further experience with cortin therapy. Hartman, F. A., C. W. Greene, B. D. Bowen and G. W. Thorn, J. A. M. A. **99**: 1478. 1932. Abst., A. M. A.

The authors emphasize the fact that when one gives a patient injections of cortical extract and gets a definite improvement within a day or two, unless the patient's illness has been very brief and quick, spontaneous changes might have been expected, one attributes such improvement to cortin. The cause of this improvement is another matter. It may be the addition of cortin to an already inadequate supply within the organism, or it may be due to the pharmacologic effect of cortin added to a normal output. Until there is available a definite means of detecting cortical insufficiency, this cannot be settled. Therapeutically, however, the interesting question is—What, if any, is the value of cortin? It has now been fairly well established that it can play an important part in the treatment of Addison's disease. It will require a great amount of work to decide its value outside of Addison's disease, because it has such a general effect on the organism. The authors believe that cortin eventually will become a useful agent to the clinician, but it will take much careful work before it will be known in what condition it is really worth while.

Progressive pseudohypertrophic muscular dystrophy: Results of treatment with adrenaline and pilocarpine, with an analysis of twenty-eight cases. Hough, G. deR., Jr., J. Bone & Joint Surg. **13**: 825. 1931. Abst., J. Nerv. & Ment. Dis. **75**: 87.

The known facts and theories in regard to the disease are reviewed and considered in detail, particularly in the light of autonomic disorder. Some cases are reported in which the type of onset suggests an infectious origin. The incidence in New England is estimated at approximately six per 100,000 population. The course of disease in the following cases was found to be as follows: Onset of symptoms between two and four years, loss of power to walk between eight and twelve, loss of use of arms twelve to eighteen years, and death from fifteen to twenty. Sixteen cases were treated with adrenaline and pilocarpine after the method of Kure and Okinaka. In eight cases there was slight improvement, in four cases there was moderate and in four cases marked. The better results were in the cases of shorter duration. No claim can be made as to the permanence of the improvement.

Detoxication and increase of effects of cardio-vascular stimulating remedies by means of atropin (Entgiftung und Wirkungssteigertung von Kreislaufmitteln durch Atropin). Keller, C. J. and H. K. Meyer, München. med. Wchnschr. **78**: 1216. 1931.

Using dogs under Pernocton anaesthesia the authors have found that vagotonic animals exhibit not only a smaller elevation of pressure than normals following the injection of adrenalin, but also show a marked bradycardia, a phenomenon not present in normal dogs. Increased doses of adrenaline result in arrythmias and even ventricular fibrillation. This is interpreted as being a toxic effect due to reflex irritation of the vagus. Such abnormalities can be abolished by the injection of atropin. The use of sympathol instead of adrenaline in itself diminishes such untoward results. The injection of sympathol plus atropin causes no unpleasant symptoms and results in a greater and more prolonged elevation of the blood pressure than sympathol alone, both in normals and in decompensated cardiac patients. The authors recommend the use of atropin with cardiac remedies such as adrenaline and digitalis, as a means of detoxication and of accentuation of the desirable circulatory effects.
—H. Freeman.

Adrenalin blood pressure curves in children (Adrenalinblutdruckkurven bei Kindern). Kruger, Edith, Monatschr. f. Kindern, **47**: 147. 1930.

In conformity with observations on adults, the author found that adrenaline gave 3 reactions recognized as normal, sympathetic and vagotonic blood pressure curves. The characteristics of the curve is not influenced by the dosage but seems to have a definite relationship to the vegetative system. Observations were made on 50 children between the ages of 4 to 15 years with various conditions but without fever. The blood pressure was taken 2 to 30 minutes after the injection of 0.5. The children reacted in three different ways. (1) The normal curve which rose slowly and within one-half hour returned to the initial figure. The maximum increase was not over 30 mm. and not under 15-20 mm. (2) The vagotonic curve had a short drop and then a slight increase which did or did not reach the normal or else it ran a flat and short course. (3) The sympathetic curve rose quickly to a very high point and continued near that level for a period of two hours at times. The incidence of the various curves was as follows: Normal, 18%; vagotonic, 30%, and sympathetonic, 52%. The effects of injection of 0.5 mgm. of atropine 40 to 50 minutes after the adrenaline was studied on both pulse frequency and blood pressure. The constant increase in pulse described by Friedberg was not obtained in every case. The blood pressure was not affected in 5, was lessened in 2 and increased in 3 instances.—M. B. G.

Suprarenal insufficiency as the cause of acute intestinal intoxication and the treatment with a suprarenal cortex extract. MacLean, A. B., R. C. Sullivan and R. L. Zwemer, Am. J. Dis. Child. **43**: 1277. 1932.

The authors claim that the following clinical picture is similar in both conditions: gastro-intestinal disturbance with diarrhea, vomiting, dehydration, dull mental state and decreased peripheral circulation. Following administration of cortical extract, the carbon dioxide capacity, chlorides, sugar and blood

non-protein nitrogen returned to normal limits. Of the 13 cases of acute intestinal intoxication treated with cortical extract, 10 were severe. With the exception of 2, all had received the usual treatment without any improvement prior to the administration of the extract. The use of the latter was followed by improvement in 8 and death in 5.—M. B. G.

Experimental production of Addison's disease (Versuche zur experimentellen Erzeugung des Morbus Addisoni). Naundorf, G., Endokrinologie, **9**: 425. 1931.

A discussion of the etiology of Addison's disease is given, and it is pointed out that the condition is generally due to lues, tumors, or gaseous tuberculosis. In cases of tuberculosis both glands, as a rule, are equally infected and the lungs are only slightly infected. The question arises as to why the focus of infection is selective for the adrenal glands. The usual explanation given is that some other weakening process leaves the adrenals open to infection, i.e., constituting a locus minoris resistentiae. According to the experimental work of Pagel and Orth adrenal glands which had previously been damaged by injections of triphal or by bruising became infected when the animals subsequently received intravenous injections of t.b. cultures, whereas in untreated animals the adrenals remained sound. Sunijoshi also showed that he was able to damage the adrenals by injections of diphtheria toxin so that upon intravenous injections of t.b. cultures the glands became a focus. Following these suggestions the author attempted to damage the adrenal glands of guinea pigs by subcutaneous doses of diphtheria toxin, saponin, and digitoxin, and then by intravenous injections of t.b. cultures to infect the glands. In no single case was a heavy tuberculosis infection found, but in eight out of the series of 37 cases tubercles could be found upon careful microscopic examination of sections.
—L. C. Wyman.

Addison's disease; further report on treatment with "interrenalin" (adrenal cortical extract). Rogoff, J. M., J. A. M. A., **99**: 1309. 1932. Abst., A. M. A.

The author describes the management of Addison's disease and its treatment with adrenal cortical extract which represents the indispensable hormone (interrenalin) of the gland. The treatment is a direct development of experimental work conducted in the laboratory and is based on the newer concept of the relation of the adrenals to the disease. Interference with the supply or function of interrenalin, from the cortex, and not epinephrine, from the medulla, is responsible for development of the syndrome. The clinical picture of adrenal insufficiency in adrenalectomized animals is quite comparable with that seen in the acute crises of Addison's disease. Recently, subacute and chronic manifestations and pathologic lesions in the adrenal glands, comparable or identical with those occurring in Addison's disease, have been successfully created in experimental animals. In both human cases and experimental animals the blood shows the same changes. There is an increase in the total nonprotein nitrogen, in urea nitrogen and particularly in the "undetermined fraction" of the nonprotein nitrogen. Blood sugar is usually only moderately diminished; calcium is frequently increased and the relative volume of corpuscles to plasma is increased. In animals there is no significant reduction in blood pressure until the acute phenomena develop. The period of good health, following total loss of the adrenal glands, ranges from one to two weeks. During this period there is no indication that the loss of the glands has affected the blood pressure. All the available evidence, from the author's experimental and clinical studies, supports the concept that the symptoms seen in Addison's disease and in adrenalectomized animals constitute manifestations of metabolic disturbances that lead to a severe intoxication. It was observed not only that these disturbances can be relieved by administering adrenal cortical extracts but also that amelioration of symptoms and prolongation of life can be effected, in adrenalectomized animals, by intravenous administration of physiologic solution of sodium chloride. Of course, this does not supply a missing hormone, and its beneficial influence can be explained only on the basis of dilution of toxic material and facilitation of its elimination. Thus, it becomes an indispensable adjuvant in the treatment of Addison's disease with extracts representing the hormone of the adrenal cortex. The comparison of cases treated with interrenalin and those under other treatment demonstrated decided prolongation of life and amelioration of symptoms in the former. Permanent relief or cure of the syndrome, however, can rarely if ever, be accomplished. Addison's disease

is the result of lack of function of the adrenal cortex (interrenalin) and not of the medulla (epinephrine). Treatment with epinephrine, therefore, is based on a concept that is not supportd by substantial physiologic evidence. Further knowledge, leading to earlier recognition of the disease, is essential.

Suprareno-genital syndrome of Cooke-Apert-Gallais (Le syndrome surréno-genital de Cooke-Apert-Gallais). Schereschevsky, N. A., Rev. franç. d'endocrinol. **9**: 105. 1931.

In a girl 12 years of age there was considerable retardation of growth (120 cm. as compared to the normal 140 cm.). She had had meningo-encephalitis some years before. There was adiposity of the face, breast and abdomen. Her features were those of an older girl. The external genitalia corresponded to those of an 18-year-old girl. The internal sex organs were atrophied. There was no menstruation. There were red spots on the gluteal region and legs. Hypertonia and tachycardia were present and there was psychical disturbance. The basal metabolic rate was minus 27%. It is probable that the cause of the disease was the meningo-encephalitis with following hydrocephalus intermus and anatomical changes of vegetative centers and secondary changes of the endocrine glands.—M. Breitmann.

The clinical picture of Addison's disease (Zur Klinik des Morbus Addison). Schmidt, R., Klin. Wchnschr. **11**: 464. 1932.

A discussion of the author's clinical experience with 25 cases of Addison's disease. The individual case histories are given in abstract. The character of the pigmentation, the changes in the distribution of hair, the asthenia, loss of weight and fatigability, the excessive febrile reaction following the injection of milk or epinephrine, the insomnia, mental irritability and pain, the gastro-intestinal disturbances, the hypotension, the rapid pulse and frequent pulsus paradoxus, the low level of the fasting blood sugar and the sensitivity to insulin, the frequent eosinophilia and the terminal clinical picture are discussed at length.—C. H. Greene.

A comparison of the chemical composition of the blood in acute intestinal intoxication and experimental adrenal insufficiency in animals. Sullivan, R. C., A. B. MacLean and R. L. Zwemer, Am. J. Dis. Child. **43**: 1279. 1932.

The chemical picture in both is that of a disturbance in salt, water and carbohydrate metabolism. Nitrogen retention, dehydration, hypoglycemia and increase in blood chlorides are the rule in both.—M. B. G.

Vitamin C, adrenaline and suprarenals (Vitamin C, Adrenalin und Nebennieren). Szent-Györgyi, A., Deutsche med. Wchnschr. **58**: 852. 1932.

The hexuronic acid isolated from the suprarenal cortex, cabbage and oranges in crystalline form is identical with vitamin C. In an experiment with 40 animals the author shows that in the first 55-day period those animals, which received 1 mgm. hexuronic acid, did not show any sign of scurvy; those receiving 1 cc. lemon juice showed some sign of scurvy, while the animals without these substances died of scurvy. The hexuronic acid was isolated from the suprarenal cortex. It has no influence on Addison's disease.—E. Kodicek.

A quantitative study of adrenal cortical hormone extraction. Pfiffner, J. J., H. M. Vars, P. A. Bott and W. W. Swingle, Proc. Soc. Exper. Biol. & Med. **29**: 998. 1932.

Extracts prepared from whole glands are more potent than those prepared from dissected cortex. Freezing the whole adrenal glands for 5 months prior to extraction has no effect upon the yield of hormone. A good yield of hormone was obtained from glands which had autolyzed for 48 hours at room temperature. Extracts preserved with 0.1% benzoic acid at 5° C. retained their activity for 6 months. Longer periods have not been studied. The stability of the finished extracts has been checked in 2 ways, (1) adrenalectomized dogs have been kept on a single batch of extract for periods of 3 to 5 months. On withdrawing extract they have come promptly into insufficiency. (2) Assayed extract has been set aside for 6 months and re-assayed without showing any loss in potency.—J. J. Pfiffner.

The effect of the adrenal cortical hormone upon the respiratory metabolism of the cat. Webster, B., J. J. Pfiffner and W. W. Swingle, Am. J. Physiol. **99**: 710. 1932.

An attempt has been made to determine the rôle of the adrenal cortex in the regulation of respiratory metabolism. Following bilateral adrenalectomy in cats, there was a maximum fall of approximately 50% in metabolism. The administration of adrenal cortical hormone to these animals caused the respiratory metabolism to return to normal in from 24 to 48 hours. This change also occurred in animals which had been subjected to total thyroidectomy prior to the beginning of the experiment. Subcutaneous injection of large amounts of the adrenal cortical hormone was not found to affect the respiratory metabolism of normal cats or rabbits. Similar quantities of the hormone, when injected into the thyroidectomized cats, caused an increase in metabolism of from 15 to 30% in 80% of the cases. It would appear that the adrenal cortical hormone exerts an influence, either direct or indirect, upon the mechanism of respiratory metabolism and that this effect can occur independently of the thyroid gland.—Authors' Summary.

Addison's disease with selective destruction of the suprarenal cortex ("suprarenal cortex atrophy"). Wells, H. G., Arch. Path. **10**: 499. 1930.

During a previous period 12 cases of Addison's disease came to the author's notice and these included 10 cases of tuberculosis of the suprarenals, 1 of amyloid disease and 1 of metastatic secondaries from a melanotic growth. There were no cases of atrophy of the suprarenals. In a later and similar period 9 cases occurred—3 of tuberculosis of the suprarenals and 6 of atrophy. These 6 cases showed a selective loss of adrenal tissue especially of the cortex, and independent of tuberculosis or any other known agency. The underlying event is a selective necrosis of the cortical cells with a lesser degree of injury to the medulla. The changes in the glands resemble those of acute yellow atrophy of the liver and a similar etiology is suggested. As both glands are affected the noxious agent must be blood spread. Age and sex appear to play no rôle. Some connection with influenza is suggested. The thyroid in general was densely infiltrated with lymphoid cells.—W. Susman.

Studies on suprarenal insufficiency. IX. Vascular responses to histamine in normal and in suprarenalectomized rats. Wyman, L. C. and Caroline tum Suden, Am. J. Physiol. **99**: 285. 1932.

Increased susceptibility to histamine in suprarenalectomized rats follows immediately the removal of the influence of the suprarenal medulla from the circulation. Direct microscopic observation of intestinal or ear blood vessels showed only dilator responses to histamine, applied directly or intravenously. Arteries, veins and capillaries dilated in the order given. The blood pressures of suprarenalectomized rats having transplanted or gross accessory cortical tissue, but no demonstrable medullary tissue were similar to those of normal rats. The blood pressures of suprarenalectomized rats having no cortical tissue were distinctly lower, indicating that the low pressure seen in suprarenal insufficiency is concurrent with cortical rather than with medullary defect. The minimal dose of histamine which would produce a detectable fall of blood pressure was about 0.0001 mgm. Little difference could be seen among the various types of rats with respect to the responses to small doses of histamine which produce small transient depressor responses (0.0001 mgm. to 0.001 mgm. per 100 grams body weight). The minimal dose of histamine necessary to produce a permanent fall of blood pressure is from 0.3 to 0.5 mgm. per 100 grams body weight for normal and control rats with sham operations, and from 0.05 to 0.1 mgm. per 100 grams for suprarenalectomized rats with or without transplanted or gross accessory cortical tissue. Subcutaneous injections of adrenaline, twice daily during seven days following suprarenalectomy, did not materially affect the vascular responses to histamine. Such slight differences as did appear were also seen in a series which received a single subcutaneous injection of adrenalin prior to the injection of histamine. It is believed that the influence of the suprarenal medulla in protecting the rat from the fatal effects of histamine poisoning is effective by virtue of the physiological antagonism between secreted adrenin and histamine, rather than that the protective action of adrenin is dependent on a continuous effect maintaining the nutrition or tone of some part of the vascular neuro-muscular mechanism.

—Authors' Summary.

The effects of insulin and other endocrine extracts on the cholesterol content of tissues. Chamberlain, E. N., J. Physiol. **70**: 441. 1930.

The cholesterol content of various tissues from 20 normal rabbits was determined as a control. Dried thyroid extract, in amounts from 20 to 76 gr. was fed over several days to 7 rabbits. This procedure did not alter the cholesterol content of any tissue, but it was noted that the general weight loss was not shared by the adrenals, from which the author suggests that the body attempts to conserve cholesterol in the adrenal cortex. Pituitrin (Parke-Davis) likewise produced no effect, either in single doses (3 cc.) nor in repeated doses over 3 to 7 days. Insulin in doses of 30 to 100 units over 3 to 6 hours, decreased the cholesterol content of the adrenal but did not affect that of other tissues. This decrease was proportional to the hypoglucemia, but if this was prevented by glucose some decrease still occurred. It is suggested that the pancreas controls the synthesis of cholesterol by the adrenal.—C. I. R.

The influence of adrenalin, pituitrin, histamine and peptones on the volume of the liver. Emery, F. E. and F. R. Griffith, Jr., J. Pharmacol. & Exper. Therap. **42**: 233. 1931.

A plethysmograph enclosing the entire liver was used and changes in liver volume were recorded by means of a tambour on a kymograph. Cats anaesthetized with ether and chloralose were used. Arterial blood pressure was taken with a mercury manometer in the usual way. The results are summarized as follows: (1) Adrenaline and pituitrin constrict the liver simultaneously with the rise in blood pressure when injected into the hepatic artery, portal or femoral vein. (2) Adrenaline dilates the liver during: (a) depressor responses in blood pressure, and (b) sometimes when pressor doses are given if the cat is in poor condition. (3) Histamine and peptone cause a diminution in liver volume which in case of histamine is probably an active contraction of the liver vessels. (4) An atypical response to histamine resulting in an increase in liver volume is discussed.—F. E. Emery.

Respiratory metabolism in metabolic diseases (Gasstoffwecksel bei Stoffwechselkrankungen). Jahn, D., Zentralbl. f. inn. Med. **52**: 1105. 1931.

An excellent didactic exposition of the physiological factors influencing respiratory metabolism in various metabolic diseases. The author points out the value of changes in gaseous metabolism in hyperthyroidism, hypothyroidism, cardiac insufficiency, diabetes mellitus, certain leukemias and disorders of the hypophysis.—J. M. Looney.

The action of pigmentary hormones in various animals (Versuche über den Wirkungsbereich von Farbwechselhormonen). Koller, G. and E. Meyer, Biol. Zentralbl. **50**: 759. 1930. Abst., Physiol. Absts. **17**: 59.

It has been shown in crustacea that the specific action of pigmentary hormones is not restricted to animals of the same species and genus. The pigments of Idotea tricuspidata can be made to spread by extracts of the eyes of Crangon vulgaris, Praunus inermis and flexuosus, and by cephalothorax extracts of both Mysis species; abdominal extracts of these animals have no effect. Extracts of Praunus inermis, like the corresponding extracts from shrimps, have an effect on the movement of melanin of Crangon. Extracts from the eyes of Crangon and Praunus inermis cause clustering of the melanin of fishes; extracts from the rostrum of Crangon cause spreading. Muscle extracts of Crangon are without effect. It has thus been shown that hormones obtained from invertebrates have an effect on vertebrates.

Influence of hormones on plants and animals after application of light (Hormonwirkung bei Pflanzen und Tier abhängig von Licht). Küstner, H., Deutsche med. Wchnschr. **58**: 625. 1932.

Prolan and insulin after application of infra-red light cause a large growth in plants. Ultra-violet light makes prolan and insulin inefficacious. Thyroxine and hypophysin are toxic for plants.—E. Kodicek.

Incretion dynamics; concerning some physiological stimuli to incretion, the pancreas and the adrenals (Inkretionsdynamik; über einige Physiologische Angreger der Inkretion der Bauchspeicheldrüse und der Nebennieren). London, E. S. and N. P. Kotschneff, Arch. f. d. ges. Physiol. **228**: 532. 1931.

An investigation of the secretions of the pancreas and the adrenals after the injection of various substances into the blood stream, using a method described in a previous paper for the collections of venous blood from the organs involved. In fasting dogs there was no evidence of insulin secretion. Intravenous injections of glucose, galactose, and of levulose increased the insulin output, as determined from the blood flowing from the pancreatic-duodenal vein leaving the pancreas. The increase of insulin was slower and less after galactose than after glucose. Tyrosin stimulated adrenaline secretion. Alanin, not chemically so closely related to this hormone, had no effect on the adrenaline secretion. Morphine was a very strong excitant of adrenaline secretion.
—L. C. Wyman.

The sugar metabolism of the liver. Second contribution. Concerning the free sugar content of the liver and its alterations under the influence of insulin and adrenalin (Der Zuckerhaushalt der Leber. Nach Versuchen an der vorgelagerten Leber; über den Gehalt der Leber an freiem Zucker und seine Veränderungen unter Insulin und Adrenalin). Molitor, H. and L. Pollak, Arch. f. exper. Path. u. Pharmakol. **162**: 488. 1931.

A liver lobe was explanted under the skin in dogs and rabbits. On the day following the operation pieces weighing 80 to 200 mgm. could be excised at short intervals from the unanesthetized animal. The liver pieces were frozen in liquid air and their free sugar extracted either by 96% alcohol or by $ZnSO_4$ solution after addition of NaOH. The non-sugar reducing substances were determined by means of yeast fermentation. In dogs fasted for 18 to 24 hours, the average true sugar of the liver was 83 ($ZnSO_4$ method) and 65 (alcohol method); in rabbits it was 97 (alcohol method). The ratio true liver sugar: true blood sugar was 0.89, 0.71 and 0.8 in the three instances. After an intravenous injection of insulin the liver sugar began to fall immediately; frequently the decline was not as rapid as that of the blood sugar. Adrenalin injection caused a rapid rise of the liver sugar. Usually the liver sugar started to drop again when the blood sugar was still elevated.—G. T. Cori.

The influence of thymus and spleen extracts (P substance) upon metabolism (Die Beeinflussing des Grundumsatzes durch Thymus und Milsextrakt [P substanz]). Nitschke, A., Monatschr. f. Kindh. **47**: 531. 1930.

Thymus and spleen extracts have the ability to lower the basal metabolic rate as shown by Schneider and Nitschke due to the presence of the P substanc of Nitschke. The injection of standardized preparations produced a fall in the basal metabolic rate of 15 to 23% and a simultaneous diminution in the excretion of nitrogenous bodies in the urine.—M. B. G.

Constitution (Konstitutionsforschung). Various authors. Endokrinologie, **10**: 79-105. 1932.

A notable bibliography of recent articles on constitution. Many of the articles are abstracted.—R. G. H.

Action of sexual hormones (ovarian and anterior pituitary) on gas metabolism (Die Wirkung von Sexualhormonen [Ovarial- und Hypophysenvorderlappenhormonen] auf den Gaswechsel). Árvay, A., Biochem. Ztschr. **237**: 199. 1931.

Commercial preparations of ovarian hormone (Menformone, Progynon, Sistomensin) showing typical estrogenic action on normal and castrated rats also induced in the same animals an increase in the basal metabolic rate, coincident with the period of induced estrus. Anterior lobe pituitary preparations had a similar effect on normal animals, also coincident with the period of induced estrus. This was followed by a depression of the metabolic rate, seen not only in normal, but in castrated and male animals as well, and hence attributed, not to the incidence of diestrus, but to a specific fraction of the anterior lobe preparation, acting in all cases to depress the basal metabolic rate.—B. S. Walker.

A case of hermaphroditism in a sheep imported from England (Hampshire short-haired meat race) (Ein Fall von Hermaphroditismus bei einem aus England eingeführten Scaf [der Hampshire kurzhaarigen Fleischrasse]). Awtokratow, D. M., Anat. Anz. **70:** 373. 1930.

A ewe sheep of five years showed the following characteristics: two testicles the size of a pigeon's egg in the subcutaneous tissue but no scrotum. There was a uterus-like formation but no paradidymis, no prostate and no glands of Cowper. The vagina was separated from the urethra only externally.
—M. Breitmann.

The probable source of the male and female sex hormones in the gonads developed in fowl after ovariectomy (Origine probable des hormones male et femelle dans les gonades développées chez la Poule après ovariectomie). Benoit, J., Compt. rend. Soc. de biol. **108:** 1195. 1931.

Removal of the left ovary in fowl is followed by an enlargement of the rudimentary right gonad. This consists of interstitial tissue and embryonal testicular cords. The former become very active and the latter show some signs of development after the operation. At this time the fowl takes on male characters. A year or so later these characters regress and the fowl becomes female in appearance. There are no histological changes except a cessation of activity in the rudimentary testicular cords. The author believes that the interstitial cells are activated to produce male sex hormone by the cords of testicular cells. After the initial activity of these cells, which never results in the production of an active testis, their influence decreases and the interstitial cells are free to produce their original type of hormone, which is female.—J. C. D.

Hemophilia. Birch, C. L., J. A. M. A. **99:** 1566. 1932. Abst., A. M. A.

During the last two years the author has had an opportunity to study 35 persons with hemophilia. They range in age from newly born to 52 years. Seven of these cases were sporadic, while 28 had a definite history. The author has traced the histories of 20 families which consist of from four to seven generations. An analysis of these histories shows that persons with hemophilia have more daughters than sons, while transmitters have more sons than daughters. Over 71% of the transmitters' sons had hemophilia. Only from 10 to 15% of the transmitters' daughters had at least one normal son and no hemophiliac sons. Of the hemophiliac daughters, only from 3 to 7% had at least one normal son and no hemophiliac sons. Nineteen patients have been receiving ovarian therapy for more than six months. Nine of these showed a good response, and nine showed definite but less marked improvement, while the condition of one remained unchanged. The response was both general and specific. The general improvement was shown by an increase in weight, hemoglobin and vitality. The specific response was shown by a decrease in number and severity of the hemorrhages and a lowering of the coagulation time. The prolongation of the coagulation time in hemophilia is due to increase in the resistance of the blood platelets, for when this resistance is overcome mechanically, the blood clots in normal time. When certain ovarian preparations are added to hemophiliac blood in a test tube, the coagulation time is decreased to one-fourth or one-half the time of the untouched control.

The source of the haemorrhages in the haemorrhagic follicles produced in young rabbits (Origine de l'hémorrhagie dans les follicules hémorragiques provoqués chez la jeune Lapine). Brouha, A., Compt. rend. Soc. de biol. **109:** 63. 1932.

Rabbits treated with the urine of pregnancy show numerous haemorrhagic follicles. The vessels of the theca form diverticula which invade the walls of the follicle from the outside inward. When these diverticula reach the lumen of the follicle they rupture. This is the essential process in the formation of these haemorrhagic follicles.—J. C. D.

Cytological changes occurring in the portions left after partial resection of the testis in mammals (Phénomènes cytologiques qui se produisent dans les nodules résiduels après résection partielle du testicule chez les Mammifères). Buchheim, W., Compt. rend. Soc. de biol. **108:** 1208. 1931.

Two-thirds of the testes and the entire epididymis were removed from guinea pigs. The remaining third was intra-abdominal. Examinations made

from 37 to 137 days after operation showed a marked enlargement in size of the interstitial cells and a steady degeneration of the tubular epithelium, with phagacytosis of its debris. There was no evidence of the conversion of other types of cell into interstitial cells.—J. C. D.

Ovarian grafts in white male rats (El comportamiento del ovario injertado en la rata blanca macho). del Castillo, E. B. and R. Sammartino, Rev. Soc. argent. de biol. **7**: 473. 1931.

Ovaries from immature and adult rats were grafted into the kidneys of normal and castrated males, adult and immature, with the following results. Immature ovaries into normal adult males, 4+, 3—; into normal immature males, 3+, 6—; into adult castrated males, 1+, 3—; into young castrated males, 1+, 8—. Adult ovaries into groups in the same order, 1+, 6—; 0+, 8—; 5+, 2—; 5+, 3—. The grafts rarely take in adult normals and even more rarely in immature males; they never form corpora lutea. In adult castrates they take more frequently and show luteinization, in immature castrates positive results are less frequent but luteinization then occurs constantly.
—J. T. Lewis.

Folliculin and clupanadonic acid (Folliculine et acide clupanadonique). Cruz Coke, E., Compt. rend. Soc. de biol. **105**: 251. 1930.

The formula suggested for folliculin is $C_{18}H_{24}O_3$. Clupanadonic acid derived from cod liver oil has the formula $CH_3\ (CH_2)_{10}\ CH_{10}\ COOH$, a non-saturated higher fatty acid. In spayed white mice injections of as little as 0.01 mgm. of clupanadonic acid gave vaginal smears characteristic of active oestrous.
—J. C. D.

Effect of theelin upon the developing ovary of the rat. Doisy, E. A., J. Curtis, and W. D. Collier, Proc. Soc. Exper. Biol. & Med. **28**: 885. 1931.

A histological study of the effect of theelin administration to immature female rats is reported. Fourteen controls and 20 experimental animals were studied. Continuous administration of small doses was found to retard the growth of the ovary almost completely. Single massive doses delayed development about 10 days.—J. M. Curtis.

Hormonal therapy in premature infants (Zur hormonal Therapie bei Frühgeborenen). Edelstein, E., Ztschr. f. Kinderh. **51**: 646. 1931.

Organotherapy has been advocated in premature infants on the supposition that the glands of internal secretion share in the general prematurity. This is given in the form of one of the following: serum from pregnant women, female sex hormone or anterior pituitary hormone. Good results have been reported by v. Raiz, Martin, v. Oettingen, Reiche and Schulze in both growth and increased resistance. Edelstein used blood from women in the 8th to 9th months of pregnancy whose Wassermann tests were negative. Starting on the second day of life, the dose consisted of 1 to 1.5 cm. of blood every second day in increasing doses up to 3 to 5 cm. The author concludes that blood from pregnant woman in this dosage has no effect on either the growth or resistance of the premature infant.—M. B. G.

Teratoma of the ovary with chorionepitheliomatous metastases as the cause of precocious puberty with a positive Aschheim-Zondek reaction (Ein Teratom des Ovars mit chorionepitheliomahnlichen Metastasen als Ursache einer Pubertas praecox mit positiver Schwangerschaftsreaktion). Fasold, H., Ztschr. f. Kinderh. **51**: 519. 1931.

A case report is given of a girl of 8 years of age who began to show symptoms and signs of precocious puberty at the age of 6 years, manifested by vaginal bleeding, increase in growth and the appearance of an abdominal tumor. Operation revealed a teratoma of the right ovary. Metastases were present in the right thyroid lobe, temple, right submaxillary region and right lung. There was hastened ossification. The urine showed a positive Aschheim-Zondek reaction. The child died a few weeks later. Similar reports of teratoma of the ovaries or testes producing precocious puberty have been made by Pick, Riesel, Michel and Oberndorfer. According to Aschheim and Zondek the positive urine reaction is positive in chorionepithelioma and in hydatiform mole.—M. B. G.

Creatin metabolism in pubertas praecox (Über den Kreatinstoffwechsel bei Pubertas praecox). Fasold, H., Ztschr. f. Kinderh. **51**: 527. 1931.

Creatin metabolism is probably related to the maturity of the sex glands. Under normal conditions, the adult has practically no endogenous creatinuria and spends his exogenous creatin in general metabolism, so that a creatinuria is not obtained until large amounts of creatin are consumed. In other words, there is a tolerance for creatin in adults. Prior to puberty, the child has an endogenous creatinuria and a decreased tolerance. The author studied the creatin metabolism in three children. One girl showed symptoms of precocious puberty due to teratoma of the right ovary (mature sex function as shown by menstruation, somatic development, and positive Aschheim-Zondek test). A boy, 5 years old, began to show manifestations of precocious puberty at the beginning of the fourth year. At the time of the studies, his precocity was evidenced in an increase in growth, hastened ossification equal to that of a 12-year-old boy, large penis and marked pubic hair. The testicles, however, were of a size normal for his chronological age. His psyche was also in keeping with the latter. There were no cerebral symptoms. The author places the eitology upon a probable pineal origin, although he candidly states that this contention may be untenable. He considers that the boy was not a true instance of pubertas praecox because of the puerile state of the testes. The third child was a normal girl of 8 years of age who was used as a control. Intravenous injection of 500 mgm. of creatin was given to all the children. Determinations made before, during and after the injection demonstrated that the girl with the true precocity of the sex glands had an adult tolerance, while the other two manifested puerile conditions. The first girl retained practically all of the ingested creatin while the latter two passed all in the urine. The administration of large amounts of ovarian hormone to a normal 8-year-old girl did not influence the puerile metabolism. The author concludes that sexual maturity accounts for the difference between adult and childhood creatin metabolism.—M. B. G.

The late changes in the secondary sex characters in cryptorchid guinea pigs after prolonged injections of urine from pregnant women (Réactions tardives des caractères sexuels secondaries du Cobaye cryptorchide après injections prolongées d'urine de Femme gestante). Foncin, A. R., Compt. rend. Soc. de biol. **108**: 1198. 1931.

Six cryptorchid guinea pigs received 30 doses of 2 cc. each daily of urine. Then, after a month's rest, 25 more doses. Two weeks later they were killed. The secondary sex characters were well developed. The seminal vesicles were larger than those of normal controls. Histologically, the walls of the seminal tubes were much thickened, the epithelial lining degenerated, but the interstitial cells numerous and actively dividing.—J. C. D.

On the mechanism of ovulation in the rabbit. V. The effect of direct intrafollicular injections of extracts of urine of pregnancy. Friedman, M. H., Am. J. Physiol. **99**: 332. 1932.

It was found to be possible to luteinize mature ovarian follicles by the direct intra-follicular injection of extracts of urine of pregnancy. By this means it is possible to produce corpora lutea unilaterally in the absence of general humoral changes of sufficient magnitude to cause any discernible change in the follicles of the opposite, untreated ovary. Corpora lutea produced in this manner suffer regression much earlier than do the corpora lutea of pregnancy or pseudopregnancy. By the means employed in these experiments it has been impossible to demonstrate any functional activity on the part of these unilateral corpora lutea.—Author's Summary.

The male hormone. Funk C. and B. Harrow, J. Biol. Chem. **92**: lxx. 1931.

An improved method of extracting comb-growth promoting substance from urine is reported. Strongly acidified urine is extracted with chloroform for 8 hours under reflux. The chloroform is separated off and residue heated under reflux for 2 hours with 20% sodium hydroxide solution. The product is repeatedly extracted with ether, the ether evaporated and the residue taken up in oil. The product usually prepared contains 10 cock units per cc. One cock unit represents the equivalent of 125 cc. of urine.—E. P. McCullough.

Menformon and lactation (Menformone et lactation). de Jongh, S. E. and E. Dingemanse, Arch, neerl. de physiol. **16**: 288. 1931. Abst., Physiol. Absts. **17**: 63.

Two hundred units menformon in oil solution injected daily into male guinea-pigs produce growth of the mammae, which secrete milk if the dose is rapidly reduced to 2 units daily. The secretion may continue for seven weeks. It resembles milk in its lactose and albumin content.

Inhibition of oestrum (Freinage du rat). de Jongh, S. E. and E. Dingemanse, Arch. neerl. de Physiol. **16**: 289. 1931. Abst., Physiol. Absts. **17**: 61.

Injections of the hormone of the anterior lobe of the pituitary gland obtained from urine of pregnancy inhibit the oestrus produced by menformon in young female rats when small doses of the latter are used. Very large doses can override the inhibiting influence. The anterior pituitary hormone has no action in young spayed females also given menformon, nor in adult animals with regular sexual cycles. It presumably acts by producing luteinization of the ovary, the inhibition of oestrus being caused by the hormone of the corpora lutea.

Male sex hormone from the urine of women (Männliches Geschlehtshormon aus Frauenurin). Kabak, J. M., Endokrinologie, **10**: 12. 1932.

Experiments were undertaken to determine whether there is present a male sex hormone in the urine of women analogous to the female sex hormone that has been found in the urine of males. This latter fact has been noted by several observers and verified by the author. The animals used in these experiments were young cocks and male guinea pigs. By observing the combs of the fowls and the seminal vesicles and prostate glands of the guinea pigs, the author noted that after castration the injection of an extract of female urine was able to compensate for the missing testicular hormone, at least in so far as the above mentioned indicators are concerned. He therefore concludes that the male and female sex hormones are found in the urine of females as well as that of males.—N. A. Womack.

Theoretical and therapeutic considerations of the problem of debility (Theoretisches und therapeutisches zum Problem der Lebensschwache). Karger, P., Jahrb. f. Kinderh. **134**: 122. 1931.

The Aschheim-Zondek test is positive in the urine of the newborn for 4 days and at times for a longer period. It is considered by some that this hormone is necessary for the nutrition of the infant and that in prematures the debility may be linked up with it due to its early deprivation and its disappearance from the urine before the 4th day. Substitution therapy both by mouth and hypodermic injection has been tried by Schiller, Martin, Mugel and Reiche with promising results as far as nutrition and increase in weight is concerned. The agents used were Unden (I. G. Farben) in solution for oral administration and Follikulin-Menformen for subcutaneous injection. Karger thinks the use of the sexual hormone in premature infants offers a fertile field. —M. B. G.

A note on the effect of theelin, theelol and the luteinizing substance on reproduction. Katzman, P. A., Proc. Soc. Exper. Biol. & Med. **29**: 700. 1932.

Prolonged administration of either theelin or theelol to adult female rats does not destroy the reproductive function, as is evidenced by their ability to bear and rear normal litters. The treatment with the luteinizing substance from pregnancy urine produces complete inhibition of estrus together with profound ovarian luteinization but does not permanently impair the reproductive mechanism—Author's Summary.

The origin of interstitial cell growth in the testes of animals treated with Prolan (Zur Entstehung der Zwischenzellenwucherung im Hoden mit Prolan behandelter Tiere). Kraus, E. J., Virchows Arch. f. path. Anat. **280**: 884. 1931.

In prolan-treated male rats the interstitial cells of the testis show an appreciable increase which, according to the author, is a primary change and not a secondary cirrhosis following atrophy of the seminiferous tubules, as is maintained by Boeters.—W. Susman.

The follicular phase in the ovary and the phase of oestrus in the vagina (Phase folliculaire ovarienne et phase vaginale oestrale). Lipschütz, A., Compt. rend. Soc. de biol. **109**: 92. 1932.

The changes in the vagina are supposed to be dependent on the changes in the ovarian follicles but, in 10 young rats injected with hypophyseal extract there were characteristic changes in the vagina and no detectable changes in the ovary.—J. C. D.

The chemistry of oestrin; the chemical nature of crystalline preparations. Marrian, G. F., Biochem. J. **24**: 1021. 1930.

Of the total oestrus-producing material in the ether extract of acidified urine 32% has been obtained as a pure crystalline substance. This substance (M.P. 264-266°) is represented by the molecular formula $C_{18}H_{24}O_3$. It is strongly dextro-rotatory. The substance is weakly acidic, being soluble in aqueous alkali. It is precipitated from alkaline solution by carbon dioxide. An acetate has been prepared. Analyses and molecular weight determinations show that three hydroxyl groups are acetylated. The acetate is insoluble in aqueous alkali. Determination of the base-binding power and approximate pH of the substance show that one hydroxyl group is acidic. Certain color reactions characteristic of phenolic substances are strongly positive. It is concluded that a hydroxyphenyl radical is present in the molecule. The activities and melting-points of the material precipitated from alkaline solution by carbon dioxide and of the material obtained by saponification of the acetate are the same as those of the original substance. The substance is not appreciably volatile at 165° and 0.001 mm. Hg. The relationship between this active substance and the active substances described by other authors is discussed.

—Author's Summary.

Grafts of vagina into male rats and observation of cycles by means of smears (Greffes de vagin sur des Rats males, et observation des cycles au moyen des frottis). Martins, T., Compt. rend. Soc. de biol. **109**: 134. 1932.

A short length of vagina is grafted beneath the skin. Two weeks later an opening is made through the skin into the lumen of the graft. This graft responds as does the normal vagina to various sex hormones.—J. C. D.

Cause of primary dysmenorrhea, with especial reference to hormonal factors. Novak, E. and S. R. M. Reynolds, J. A. M. A. **99**: 1466. 1932. Abst., A. M. A.

The authors point out that many theories have been offered to explain the etiology of primary dysmenorrhea, and many plans of treatment have been suggested. None has seemed adequate, although the importance of psychogenic, constitutional and other such factors in the causation of many cases is undoubted. The immediate cause of the pain, on the basis of the physiologic studies reported by the authors, is almost surely a disturbance of the normal motility factors of the uterine muscle. In general, female sex hormone or theelin is an excitant and progestin inhibitor of this motility. Preparations of the urine of pregnant women, presumably because of their prolan content, likewise are strongly inhibitory. The inhibitory influence of progestin on uterine motility is removed a day or two before the menstrual onset, and the withdrawal of this restraining factor produces dysmenorrhea in some women, possibly those with such predisposing factors as constitutional subnormality or phychoneuroses. In other cases it would seem that there is an actual imbalance between the theelin and progestin, either quantitative or chronological, or both.

Contributions on the presence and the effect of female sex hormones (Beiträge zum Vorkommen und zur Wirkung der weiblichen Sexualhormone). Schwerdtfeger, H., Arch. f. exper. Path. u. Pharmakol. **163**: 487. 1931.

Using the usual Allen-Doisy technique experiments were made to test for the presence of oestrogenic material in the lower types of animals. Experiments were also made on the surviving uterus strip with alcoholic extracts from the same sources. Oestrogenic material was found in coelenterates and arthropods.—L. C. Wyman.

Pregnancy changes in the rabbit's uterus and their relation to endocrine activity. Robson, J. M. and R. E. Illingworth, Quart. J. Exper. Physiol. **21**: 93. 1931.

The statement of Knaus, that the injection of an extract of the corpus luteum into mature non-pregnant rabbits inhibits the in vitro reaction of the uterus to pituitrin, has been confirmed. Both the oxytocic and pressor fraction of the posterior lobe are inhibited. Small doses of alpha (oestrin, in oily solution) do not interfere with the progestational or inhibitory reactions of the corpus luteum hormone; large doses of alpha (more than 3000 mouse units) prevent the progestational reaction, but the pituitrin reaction is still inhibited. Inhibition of the pituitrin reaction was obtained in several cases with an extract of the human placenta. No proliferation was obtained. The corpus luteum extract was partitioned between petroleum ether and 50% alcohol. The petroleum ether fraction caused proliferation, but little or no inhibition. The 50% alcohol fraction, which formed a colloidal solution in water, caused some proliferation and complete inhibition. Saponification destroyed both the proliferative and inhibitory actions of the corpus luteum extract. It is suggested that the proliferative and inhibitory actions of the corpus luteum extract may be due to different factors.—Authors' Summary.

The effect of various methods of administration of pregnancy urine on the ovary of the rat. Shelesnyak, M. C. and E. T. Engle, Anat. Rec. **53**: 243. 1932.

An attempt was made to discover any differences in ovarian reactions of the rat to maximal and minimal rates of absorption of active anterior pituitary-like principle of urine of pregnancy. A highly concentrated solution of pregnancy urine was introduced by intracardiac route in order that the probabilities of immediate maximal absorption would be great. Capsules of loose dry powder effected slower absorption. The rate was further decreased by the use of solid compact spherical pills subcutaneously introduced. By these methods differential absorption rates were approximated. Attempts to provoke superovulation in adult rats at late proestrus with intracardiac injection of pregnancy urine failed. Ovulation occurred in young rats at the vaginal opening after injections of pregnancy urine, but was not constant enough to be significant. Responses to dried powder of urine concentrate showed no consistency. With slow rates of absorption extensive luteinization occurs, but "blood points" occur very rarely, demonstrating that these phenomena in the rat are due to the rate of absorption of the active principle.—Authors' Abst.

Crystallographic description of theelol. Slawson, C. B., J. Biol. Chem. **91**: 667. 1931.

The crystals are monoclinic forming rectangular parallel epipeds. The crystals are optically negative; the indices of refraction are alpha $=1.533$, beta $=1.642$, and gamma $=1.686$ (all $\pm$ 0.003); and 2V is approximately 60°. The extinction angle is 5½°, measured from the longer edge of the rhomboid in the direction of the obtuse angle. Alpha is measured parallel to this direction and beta perpendicular to it.—S. A. Thayer.

The comparative sensitivity of the reproductive tracts of hypophysectomized and ovariectomized rats to follicular hormone. Smith, P. E., Am. J. Physiol. **99**: 349. 1932.

The comparative sensitivity of the uteri and vaginae of hypophysectomized and ovariectomized rats to injections of follicular hormone has been studied. No essential difference has been found. The response of the vagina as regards the free cell types and the structure of its epithelium and of the uterus as regards its weight and structure was always as great and not infrequently greater in animals which were hypophysectomized than it was in those which were ovariectomized. These findings are harmonious with other experimental work in rodents, which has failed to show any direct interrelationship of the vagina or uterus with the anterior hypophysis.—Author's Summary.

Basal metabolism of normal children: the puberty reaction. Topper, A. and H. Mulier, Am. J. Dis. Child. **43**: 327. 1932.

The basal metabolism of 28 girls and 10 boys from 10 to 16 years of age was studied at intervals of six months to a year over a period of from one to four years. It was found that there was an increase in the basal metabolic rate in the prepubescent period, reaching its maximum around the time when catamenia was established in girls, and sexual maturity in boys, with a subsequent decline afterward. There was no uniformity in the height of the increased metabolism, or in the duration of the increase. Some of these children had no other symptoms of an overacting thyroid gland. Others presented such symptoms as an enlarged thyroid gland, tremor, nervousness, vasomotor instability, cardiac murmur and tachycardia—all of which symptoms disappeared as the basal metabolic rate returned to the previous normal level, when puberty was well established. The authors believe that an increased basal metabolism is physiologic during pubescence. This increase coincides with the physiologic age rather than with the chronological age, and occurs earlier in girls than in boys, coincident with their earlier pubescence.—M. B. G.

The effect of theelin and theelol on the growth of the mammary gland. Turner, C. W., A. H. Frank, W. U. Gardner, A. B. Schultze and E. T. Gomez, Anat. Rec. **53**: 227. 1932.

Experiments are recorded which indicate that the two purified estrogenic hormones, theelin and theelol, stimulate the growth of the duct system of the mammary glands of the rabbit, rat, and mouse. No significant difference was observed in the type of duct growth produced by theelin, theelol, or the crude estrogenic extract recovered from the urine of pregnant dairy cattle. The slight proliferation of lobules which has been observed following the extended injection of the crude extract in the rabbit and rat was not observed during the course of these experiments.—Authors' Abst.

A case of hermaphroditism in a child. Vinogradoff, P. P. and A. L. Froloff, Anat. Anz. **68**: 4; 91. 1929.

There was a rudimentary penis consisting of four crooked parts formed by connective tissue without any opening. There was one testicle under the skin of the abdomen and the other in the abdominal cavity. There was a rudimentary uteris with a cervical channel 2.5 cm. in length. The vagina was 2.5 cm. long and 2.2 cm. wide. Ovaries and tubes were not present.
—M. Breitmann.

The detection of the anti-diuretic component and the pressor substance of the posterior lobe of the hypophysis in the blood in nephrosis of pregnancy and eclampsia (Nachweiss der antidiuretischen Komponente des Hypophysenhinterlappenhormons und einer blutdrucksteigernden Substanz im Blute bei Nephropathie und Eklampsie der Schwangeren). Anselmino, K. J. and F. Hoffmann, Klin. Wchnschr. **10**: 1438. 1931.

An ultrafiltrate at a pH of 3.9-4.3 was prepared from the citrated plasma of the blood of nephrosis of pregnancy and eclampsia. These ultrafiltrates caused a marked antidiuresis in rabbits. The chemical, physical and pharmacological properties of the anti-diuretic hormone of the pituitary are similar to the antidiuretic substance found in blood in nephrosis and eclampsia. The pressor substance in the ultrafiltrate causes a decided sustained increase in the blood pressure and is similar to the pressor component of the pituitary in that the second injection is less effective than the first. The authors believe that the pituitary hormones and the substances in the blood are identical.—E. L.

Note on the technic of detecting and measuring small amounts of "thyreo-stimuline" from the anterior lobe of the hypophysis when present in blood or urine (Note de technique sur la mise en évidence et l'évaluation quantitative des faibles taux de "thyreo-stimuline" prehypophysaire presénts dans le sang ou l'urine). Aron, M., Compt. rend. Soc. de biol. **109**: 218. 1932.

Guinea pigs of 150 to 220 grams were injected subcutaneously or intraperitoneally. Five cc. of urine or blood was given daily for 3 days and the animals killed 24 hours later. The thyroid was fixed in Zenkers fluid and section 3 to 4 micra thick examined. Urine and blood from normal persons give a distinct stimulation of the center of each lobe.—J. C. D.

Sexual reactions of certain anurans after anterior lobe implants. Bardeen, H. W., Proc. Soc. Exper. Biol. & Med. **29**: 846. 1932.

Mature female leopard frogs (Rana pipiens) were made to ovulate out of season a second time within two months following homoplastic implants of anterior pituitary.—Author's Summary.

The surfaces of contact between the different parts of the pituitary and the neuro-hypophysis in guinea pigs (Les surfaces de contact entre les différentes parties de la gland pituitaire et la neurhypophyse chez le Cobaye). Collin, R. and M. Weis, Compt. rend. Soc. de biol. **109**: 123. 1932.

The pars intermedia covers a large part of the surface of the pars neuralis. The pars tuberalis covers one-seventh, while the pars anterior covers one-twelfth of the surface of the pars neuralis. Over one-third of its surface is not in contact with any other part of the gland.—J. C. D.

The counteractive effect of tribromethanol (Avertin) on the stimulatory response to pituitrin injected in the ventricle. Cushing, H., Proc. Nat. Acad. Sc. **17**: 248. 1931. Abst., Arch. Neurol. & Psychiat. **27**: 195.

In this paper, the fifth contribution of Cushing on the effect of injection of solution of pituitary into the ventricle, an attempt is made to determine further the action of this substance and of pilocarpine on the brain stem. In a previous study it was found that in tumors of the interbrain no response is obtained by the injection of solution of pituitary or pilocarpine. This argument is used, therefore, in favor of the view that these substances act on the hypothalamic nuclei. In order to test this hypothesis further Cushing sought for a narcotic inhibiting the thalamencephalic centers and for this purpose used tribromethanol which, like dial Ciba, acts on the subcortical centers. The drug, produces deep, apparently natural sleep, pupillary contraction and fall in blood pressure. If these are essential in origin, the sleep is assumed to be due to stimulation of the sleep center. Tribromethanol is antidotal. Two patients were observed, in each of whom there was a typical reaction to solution of pituitary injected into the ventricle while there was no reaction with the patient under tribromethanol. It was therefore concluded that tribromethanol "presumably causes its effects by action on centers of the diencephalon, and serves to counteract the stimulatory responses to pituitrin injected into the ventricles."

Concerning a possible "parasympathetic center" in the diencephalon. Cushing, H., Proc. Nat. Acad. Sc. **17**: 253. 1931. Abst., Arch. Neurol. & Psychiat. **27**: 195.

The conclusions reached by Cushing in this series of investigations may be summed up as follows: (A) The active principle of the neurohypophysis is excreted in part into the blood stream and in part into the cerebrospinal fluid. The hormone when experimentally introduced into the blood stream causes pallor from vasoconstriction and stimulates the musculature of the lower bowel; when introduced into the ventricle, on the contrary, it causes flushing, sweating, salivation, lacrimation, vomiting and a pronounced fall in body temperature. The former reaction bears resemblance to a sympathetic discharge combined with the sacroautonomic effect; the latter appears to be essentially a cranial autonomic or parasympathetic effect. Pilocarpine introduced into the ventricle gives a highly similar response. These responses to intraventricular injections of solution of pituitary and pilocarpine are counteracted by atropine, whether given subcutaneously or intraventricularly; they, moreover, appear to be abolished when the tuberal portion of their action, furthermore, is checked by tribromethanol, a narcotic that presumably acts chiefly on the interbrain. (B) A rich arborization of unmyelinated nerve fibers is known to pass from the tuberal nerve centers to ramify in the neurohypophysis. The posterior pituitary hormone or a substance indistinguishable from it has been shown to be increased in the cerebrospinal fluid after electrical stimulation of the tuber. It has also been shown to be increased in amount in the fluid in animals under emotional excitement. The interbrain has been shown to be the seat of the primitive emotions that are released from their cortical inhibitions by experimentally disconnecting the nerve paths from the frontal cortex. Theoretically, animals so decorticated should show an increase of posterior pituitary hormone in the cerebrospinal fluid. (C) As a working concept it may be assumed: (1)

that under emotional stimuli the posterior pituitary hormone becomes discharged through its specific and histologically demonstrable thalamencephalohypophyseal mechanism; (2) that the active principle or a portion of it enters the cerebrospinal fluid, whence, presumably by diffusion through the ependyma, it may come to act on thalamencephalic nuclei from the parasympathetic apparatus, and (3) that conditions may conceivably arise in which posterior pituitary hormone is discharged into the fluid in sufficient strength to call forth a parasympathetic (cranial autonomic) response as diffuse in its character as is the response on the part of the sympathetic system brought about by the discharge of epinephrine. The neurohypophysis, in short, may conceivably bear a somewhat similar relation to the parasympathetic division as the suprarenal medulla bears to the sympathetic division of the autonomic nervous system.

The influence of the pituitary on the activity of striped muscle (Uber den Einfluss der Hypophyse auf die Tätigkeit des quergestreiften Muskels). Deuticke, H. J., Pflüger's Arch. f. d. ges. Physiol. **227**: 24. 1931.

A fatigue curve of one gastrocnemius muscle in a series of frogs in the normal state (except the blood vessels were occluded during stimulation) were compared with the fatigue curve in the corresponding muscle of the opposite limb of the same animal under the same conditions from one to ten days after hypophysectomy. In a second group the fatigue curves of a gastrocnemius in hypophysectomized frogs were compared with the opposite muscle as above (a) after the injection of an extract from the anterior lobe of the pituitary and (b) after injection of an extract from the posterior lobe. The results show that after total hypophysectomy in frogs there was muscle weakness exhibited by quicker exhaustion and a lower amplitude of the fatigue curve in isotonic and isometric contraction. In a series of hypophysectomized frogs which were injected daily for seven days with extracts from the anterior or posterior lobe of the pituitary there was an improved condition in the fatigue curves. The gastrocnemius muscle curves of normal frogs showed no improvement after injecting hypophyseal extracts.—L. B. Nice.

Different pars tuberalis disorders occurring in several members of a single family (Troubles hypophysotubériens divers apparus chez plusieurs membres d'une même famille). Etienne, G. and G. Richard, Rev. franç. d'endocrinol. **8**: 521. 1930.

The author believes the cases cited indicate an inheritable condition in dysfunction.—B. C.

Relation of Prolan to the anterior hypophyseal hormones. Evans, H. M., K. Meyer and M. E. Simpson, Am. J. Physiol. **100**: 141. 1932.

Prolan in amounts sufficient to produce maximum ovarian weight increase (approximately 60 mgm. in 100 hours), numerous corpora lutea and large follicles, was administered in combination with anterior hypophyseal preparations in amounts just below or equal to the dosage previously found to provoke precocious maturity in young rats. The combination produced ovaries weighing far more than those produced by either preparation alone, or than could have been expected from an additive effect. This was not the case when Prolan was combined with inactivated (heated) anterior lobe extract or with a similarly prepared liver extract. Anterior lobe extracts were resolved into growth and gonad-stimulating hormones and each administered with Prolan, an activation effect being obtained only with the growth hormone. The authors conclude that this effect is specific, and that it involves the conversion of an inactive hypothetical prohormone (possibly the growth hormone) by Prolan into an active substance which possesses gonad-stimulating properties.

—Minna Emch.

Xanthoma multiplex; two cases involving larynx and trachea, and associated with diabetes insipidus. Finney, W. P., H. Montgomery and G. B. New, J. A. M. A. **99**: 1071. 1932. Abst., A. M. A.

In two cases of xanthoma multiplex observed by the authors, the distribution of the cutaneous lesions was similar and tended to involve flexor surfaces and protected areas. This is in contrast to most cases of xanthoma tuberosum

multiplex or xanthoma diabeticorum, in which lesions are more commonly found on exterior surfaces and areas exposed to trauma. Both patients had mild diabetes insipidus controllable by solution of pituitary; in one case surely, and in the other case probably, the appearance of xanthoma preceded the onset of polyuria; in neither was any tendency shown for the polyuria to progress in severity. When diabetes insipidus occurs together with xanthoma, it is usually assumed that a xanthomatous deposit has occurred in the region of the pituitary gland or the floor of the third ventricle. This has been proved in at least one case. It may also be noted that neither of these patients had any chronic disease affecting lipid metabolism nor was there any chemical abnormality demonstrable in the blood. Slight deficiency of hemoglobin and slight leukocytosis existed in both cases. Both patients complained of decrease in ambition and energy of moderate degree; the explanation of this is not apparent. The authors were not able to alter the appearance of the cutaneous lesions by methods which have occasionally been attended by success in the hands of others.

A case of an intrasphenoidal tumor of the hypophyseal tract (Ein Fall der intrasphenoidalen Hypophysenganggeschwulst). Garschin, W., Ztschr. f. Krebforsch. **31**: 432. 1930.

In a man 50 years old there was found a carcinoma of the sphenoid bone. The tumor protruded into the skull cavity and into the throat. Metastases were found in lymph nodes and in the liver. The tumor was assumed to be a choristoblastoma from epithelial rests of the hypophyseal tract. The hypophysis was displaced and compressed. Clinically, only signs of brain and nerve compression were noted.—M. Breitmann.

Cell changes in the anterior lobe of the pituitary following cancer transplantation in rats. Guyer, M. F. and P. E. Claus, Anat. Rec. **52**: (No. 3). 1932.

After successful transplantation of carcinoma into their body walls, both male and female rats show the characteristic increase of anterior-lobe basophiles, even to the point of vacuolization, that follows castration. The Golgi apparatus, prominent in both basophiles and oxyphiles, is associated with formation of the vacuolar material in the basophile cells of cancerous and of castrate rats. The transplanted anterior-lobe substance of both cancerous and castrate rats stimulates ovarian growth and sexual precocity in young rats and mice, although that of cancerous castrates is more potent than that of castrates alone.—Authors' Abst.

The hormonal-nervous regulation of anterior pituitary secretion (Die hormonal-nervöse Regulierung der Funktion des Hypophysenvorderlappens). Hohlweg, W. and K. Junkmann, Klin. Wchnschr. **11**: 321. 1932.

The internal secretion of the gonads and of the anterior pituitary are regulated through a nervous center. The "sex center" controls the activity of the anterior pituitary in the sense that when a decrease in the sex hormone concentration of the nervous centers occurs, the pituitary is stimulated to increased activity. This, in turn, causes an increased production of hormone by the gonads.—M. O. L.

Pituitary anterior lobe and gonads (Über die Beziehungen zwischen Hypophysenvorderlappen und Keimdrüsen). Hohlweg, Y. and M. Dohrn, Klin. Wchnschr. **11**: 233. 1932.

Large vacuole cells appear in the anterior pituitary after castration. These disappear after injection of progynon. The pituitary hormone regulates the secretion of the ovarian hormone and the latter in turn regulates secretion of the anterior hypophysis. That castration causes an overproduction of the anterior lobe hormone is shown in parabiotic experiments (union of a castrated with a non-castrated female rat). Oestrus appears rapidly in the non-castrated. After injection of folliculin into the castrated rat, however, no oestrus appears.
—E. Kodicek.

Weight of thyroid in hypophysectomized dogs (Hipófisis y tiroides. I. El peso de la tiroides de los perros hipofisoprivos). Houssay, B. A., A. Biasotti and P. Mazzocco, Rev. Soc. argent. de biol. **7**: 428. 1931.

The thyroid weight of dogs was determined (58 normal, 49 hypophysectomized) some time previously. The thyroid weight was also determined in 21 recently hypophysectomized and in 17 with lesions in the tuber cinereum. Wide variations were observed in all groups. After recent hypophysectomy and simple craniotomy no difference from the normal was observed. Some time after hypophysectomy there is a definite atrophy of the thyroid, especially if the operation is performed in young puppies. Lesions of the tuber cinereum produce a slight decrease in thyroid weight, but no microscopical alterations. —J. T. Lewis.

Microscopical anatomy of thyroid of hypophysectomized dogs (Hipófisis y tiroides. II. Histología de la tiroides de los perros hipofisoprivos). Houssay, B. A., A. Biasotti and A. Magdalena, Rev. Soc. argent. de biol. **7**: 437. 1931.

Lesion of the tuber cinereum is followed a few days after by a transitory stage of hyperactivity. There is reabsorption of colloid, cuboid or cylindrical epithelium, which in places is shed within the follicle. In hypophysectomized dogs a similar picture is seen on the days immediately following operation; 10 to 30 days later the gland shows signs of lowered activity, the epithelium becomes flat, the cells and nuclei smaller, the follicles are large in size, and appear dilated and in parts the interfollicular septa are broken. Extirpation of the posterior pituitary lobe and simple craniotomy do not influence the thyroid's structure.—J. T. Lewis.

Iodine in thyroid of hypophysectomized dogs (Hipófisis y tiroides. III. El yodo de la tiroides de los perros hipofisoprivos). Houssay, B. A., A. Biasotti and P. Mazzocco, Rev. Soc. argent. de biol. **7**: 447. 1931.

Twelve dogs were hypophysectomized 33 to 156 days before the experiment. They showed iodine in the thyroid, maximum 185, minimum 49, average 99 mgm. per 100 gram. Sixteen normal controls showed iodine in the thyroid; maximum 128, minimum 33, average 59 mgm. per 100 gm. The total amount per gland was similar in both groups. Hypophysectomized (average) 1.12 mgm., normal 1.10 mgm. per gland.—J. T. Lewis.

A histological study of the ox pituitary gland after freezing and exposure. Howes, N. H., J. Exper. Biol. **7**: 253. 1930.

A histological method is described for a study of post-mortem cytoplasmic changes; the method depends upon observed variations in staining capacity. By the application of this method, a series of cytoplasmic changes were found in ox pituitary glands which had been exposed, after the death of the animal, for varying times to different temperatures. These changes correspond to alterations in the biological activity and chemical content previously investigated. These methods showed that freezing apparently causes no alteration in the distribution of biological activity. It is possible that the histological appearance can be used to determine the suitability of ox pituitary glands for the preparation of active extracts of the anterior lobe.

The use of the modified Aschheim-Zondek test for pregnancy. Kincaid, H. L. and H. J. Rafn, South. M. J. **25**: 503. 1932.

Forty-five cases were examined by the Friedman modification. In 39, the test agreed with the later clinical history. Three patients, who gave positive results, menstruated shortly afterward. It is suggested that this menstruation really involved a miscarriage. Three pregnant women failed to show a positive test.—J. C. D.

The pituitary factor in arteriosclerosis; its experimental production in rabbits. Moehlig, R. C. and E. A. Osius, Ann. Int. Med. **4**: 578. 1930.

The importance of suprarenal cortex hypertrophy in arteriosclerosis, hypertension and nephritis makes the suprarenal cortex hypertrophy found in our injected animals of great significance. By the injection of posterior lobe extract

alone, without the influence of diet, we are able to produce a suprarenal cortex hypertrophy, an important link in the chain of arteriosclerosis. Marked production of atheromatous plaques in the rabbit's aorta may be produced within one hundred days by feeding a diet high in cholesterol and the daily injection of posterior lobe pituitary extract.—Authors' Summary.

The excretion of hormone in childhood (Die Hormonausscheidung in Kindersalter). Neumann, H. O. and F. Peter, Ztschr. f. Kinderh. **52**: 24. 1931.

In their previous work the authors reported the presence of anterior pituitary hormone in the cord blood and urine in the new-born 1 to 11 days old and in older children 3 months to 10 years old. Previously to this Aschheim and Zondek and Fels demonstrated that anterior pituitary hormone was found in cord blood. Phillip and Bruhl found the same in urine in new born. An extensive review of the literature is given. Based upon the results of 318 tests in the new-born up to the 11th day, they conclude that the anterior pituitary hormone is present in decreasing amounts in this period. The oestrus producing hormone is thrown off or disappears earlier than the anterior pituitary hormone and was not found after the third day. The test for anterior pituitary hormone in the urine of children between 1 and 10 years of age showed that the anterior pituitary hormone is thrown off by the blood in so small a quantity that it does not appear constantly in the urine. The ovarian hormone is not thrown off at all, at least not in appreciable amounts. Based upon experimental data the authors feel that the fetal blood contains an ovarian hormone which produces swelling of the mammary gland in the new-born and that mammary milk appears when there is a complete disappearance of ovarian hormone from the body of the new-born which is about the fourth day.—M. B. G.

Concerning the histology and endocrine function of the anterior lobe of the pituitary (Über den Zusammenhang von Histologie und innersekretorischer Wirkung des Hypophysenvorderlappens). Philipp, E., Zentralbl. f. Gynäk. **54**: 3076. 1930.

Ninety-nine human pituitaries (fetal to adult) were studied histologically and by implantation into immature female mice. In some cases only one procedure was possible. When pituitaries obtained from fetuses were implanted a slight stimulation of follicle formation and some enlargement of the uterus (anterior pituitary I or Prolan A effect) were obtained. Such pituitaries contain mostly undifferentiated cells among which are found a few eosinophiles but no basophiles. With pituitaries from newly born children entirely similar effects were obtained. In such glands eosinophiles are more numerous; only a few basophiles are present. Implantation of glands from infants in the first year gave similar results. Pituitaries of children 3-9 years old when implanted caused a very marked anterior pituitary I effect. Histologically these glands show a decided increase of chromophile cells, especially eosinophiles. Pituitaries from adults (exclusive of pregnancy) gave not only effect I but also formation of corpora lutea atretica and luteinization of follicles (Prolan B effect). To the eosinophile cells must be ascribed the Prolan A effect. The relation of the basophiles to follicle luteinization is questionable since the effect is sometimes obtained with pituitaries containing very few basophiles. The author holds, however, that two different hormones affecting the ovary are produced in the pituitary.—W. J. A.

Blood amino acid and blood sugar curve following glycocoll injection in hypophysectomized dogs (Aminoacidemia experimental e hiperglucemia por inyección de glicocola en los hipofisoprivos). Re, P. M., Rev. Soc. argent. de biol. **7**: 503. 1931 .

In half the hypophysectomized animals there was a slightly retarded blood aminoacid curve. A similar occurrence was observed only once in dogs with lesion of the tuber. Fasting blood sugar is low in hypophysectomized dogs and in those with tuber lesions The injection of glycocoll produces a greater and more prolonged hyperglycemia in hypophysectomized dogs than in the other two groups.—J. T. Lewis.

Hypophyseal cachexia (Simmonds' disease). Riecker, H. H. and A. C. Curtis, J. A. M. A. **99**: 110. 1932. Abst., A. M. A.

The authors state that in 1914 Simmonds reconstructed from necropsy studies of two cases the clinical syndrome which results from destruction of the anterior lobe of the hypophysis. Since that time a number of cases have been described in the German literature, although none appeared in the English language until Graham and Farquharson reported four cases in 1931. Clinically, the syndrome is characterized by premature senescence, generalized atrophy of all tissues, gradual failure of the body functions, mental torpor, apathy and death. The basis of symptoms of Simmonds' disease is progressive atrophy of tissue. Weakness, loss of weight, rapid aging, falling hair, anorexia and loss of sexual function are prominent symptoms. An initial polyuria and polydipsia are frequently early symptoms. The loss of sexual function is always present and is usually an early symptom. These two conditions are prominent in other diseases of the hypophysis and they serve only to direct attention to this gland. Physical examination shows a shiny dry atrophy of the skin, sometimes confused with that of the thin subject of myxedema, a loss of body hair, the marked loss of weight, but most strikingly the premature aging of the patient. In men the testes are atrophic, the beard is scanty, the voice is hollow, and muscular strength is greatly diminished. An underlying pathologic process (i.e., syphilis, tuberculosis) often masks the conditions found with the exception of the premature senility. In addition, there is a definitely lowered basal metabolism, marked secondary anemia, and often a disturbance of the sugar metabolism. The prognosis is by no means fatal, particularly in cases resulting from syphilis. The authors report three cases of this condition. An ambulatory case, in a man, aged 47, was characterized by an initial diabetes insipidus, premature senility, low basal metabolism and generalized atrophy. The history and serologic observations suggested syphilis as the etiologic factor. A second case showed many characteristics of Simmonds' disease due to a tumor of the pars intermedia (malignant adenoma of the pars intermedia). In a third case characterized by premature senility, syphilis was the etiologic factor.

Neurohypophysis and erection (Neuro-ipofisi ed erezione). Roasenda, G., Riv. di pat. nerv. **37**: 75. 1931. Abst., Arch. Neurol. & Psychait. **27**: 458.

The author reports the clinical history of a syphilitic patient suffering from incontinence and absolute loss of sexual stimuli and erection for almost two years. The author tried several pituitary preparations and found that solution of pituitary (Parke Davis) had an immediately beneficial effect in the re-establishment of the bladder function and immediate erection after every injection. Later, the sexual function gradually returned to normal. The author is inclined to believe that the solution of pituitary acted on the sympathetic hypogastric plexus and directly on the unstriped musculature of the bladder and of the cavernous bodies.

The effect of the growth hormone on the brain weight-body weight ratio. Rubinstein, H. S., Anat. Rec. **53**: 265. 1932.

Five groups of adult female white rats (Mus norvegicus albinus) were used in this study. All animals were kept under similar experimental conditions. The experimental animals were subjected to daily (except Sunday) 2-cc. intraperitoneal injections of an alkaline extract of the anterior lobe of beef pituitary glands. Each experimental animal had two litter-mate sisters as controls, one of which received a meat extract while the other remained uninjected. At the end of a ten-week period, by which time the experimental animals had gained 100 grams or more in body weight, all injections were stopped and the animals sacrificed at varying intervals. It was found that the brains of the experimental group failed to gain weight in proportion to the rest of the body. It was concluded on the basis of these experiments that the growth hormone fails to affect the rate of brain growth to the same extent as it does the growth of the body. Hence, under this treatment, the brain weight-body weight ratio is diminished.—Author's Abst.

Influence of anterior pituitary substances on the total iodine content of the thyroid gland in the young duck. Schockaert, J. A. and G. L. Foster, J. Biol. Chem. **93**: 89. 1932.

The treatment of 6 young male ducks with a fresh saline emulsion of beef anterior pituitary induced a rapid drop in the total iodine content of the thyroid gland. The total iodine content is as low after a week as after 5 weeks of treatment (one-tenth to one-twentieth of the normal). The percentage of iodine continued to drop more and more as the glands developed a marked hypertrophy and hyperplasia. The anterior pituitary fraction which contained the growth hormone [van Dyke and Wallen-Lawrence's phyone (3 cases)] also showed this thyrotropic action.—R. G. H.

The secretory capacity of the anterior hypophysis as evidenced by the effect of partial hypophysectomies in rats. Smith, P. E., Anat. Rec. **52**: (No. 3). 1932.

The effects of partial ablation of the anterior hypophysis on general body growth, the thyroids, adrenals, reproductive organs, and reproduction have been studied in rats. The weights of fragments of the anterior hypophysis at autopsy varied from 10 to 90% of the weights of this gland in littermate controls. General body growth, as determined by weight and total length, and weights of the thyroids, adrenals, and gonads were normal in those animals in which a fragment of the anterior pituitary equal to 30% or more of the weight of this gland in the controls was found at autopsy. When distinctly less amounts were present, there was dwarfing and the glands were below the weight of those in the controls. Ten per cent of the anterior pituitary (about 1 mgm.), however, prevented the full development of disabilities invariably appearing in total ablations. No structural abnormalities of the thyroid and adrenals were found even in those animals which had the smaller amounts of anterior hypophysis. The ovaries, on the other hand, showed a decrease in the number of follicles and corpora lutea in the more complete ablations, and sex cycles were irregular. They were normal when 30% of the anterior hypophysis was present, as were also sex cycles, mating, and reproduction. The results show that in the rat the anterior hypophysis has a large margin of safety.
—Author's Abst.

The non-essentiality of the posterior hypophysis in parturition. Smith, P. E., Am. J. Physiol. **99**: 345. 1932.

The posterior hypophysis was removed in adult female rats and the effect upon parturition noted. The completeness of the ablation was verified by a microscopic examination of serial sections of the pituitary capsule and its contents. In all cases some anterior lobe tissue was also removed but a sufficient amount remained to maintain normal body growth and sex cycles. Six of these animals were mated and bore litters. Birth occurred at the usual time. The evidence thus shows that in rats a secretion of the posterior hypophysis is unnecessary either for the genesis or the maintenance of the uterine contractions at parturition.—Author's Summary.

The effect of castration on the capacity of the hypophysis to induce ovulation. Wolfe, J. M., Am. J. Anat. **50**: (No. 3). 1932.

A saline suspension was prepared from fresh anterior-lobe tissue of normal female rats and rabbits and of castrated female rats and rabbits. One cc. of the suspension was equivalent to 1 mgm. of fresh tissue. This suspension was injected into the marginal ear vein of sexually mature female rabbits. It was found that in the rats, removal of the ovaries caused a hypertrophy of the anterior lobe, associated with a marked increase in its capacity to induce ovulation in the rabbit. In the female rabbit there was no appreciable hypertrophy of the anterior lobe after castration, and no increase in the capacity of the anterior lobe to induce ovulation.—Author's Abst.

The use of the rabbit in the Aschheim-Zondek test for pregnancy. Wood, Martha A., South. M. J. **25**: 508. 1932.

In 93 cases, the test agreed with the clinical findings 89 times. Thirty-three of these tests were controlled by re-inoculation of the rabbit with the suspected urine and a reading of the ovaries 48 hours later, as described by Reinhart. In these 33 cases, the test was 100% accurate.—J. C. D.

Bromine in the hypophysis and its relation to age (Der Bromgehalt der Hypophyse und seine Beziehungen zum Lebensalter). Zondek, H. and A. Bier, Klin. Wchnschr. **11**: 759. 1932.

In the hypophysis there is 15-30 mgm. per cent of bromine. In women of 45-60 years there is only 15 mgm. per cent, and in men and women older than 60 years there is less than 5-6 mgm. per cent.—E. Kodicek.

The hormone of the pars intermedia of the hypophysis (Intermedin) II. Intermedin in the organism (hypophysis, brain). (Hormon des Zwischenlappens der Hypophyse [Intermedin]; Intermedin im Organismus [Hypophyse, Gehirn]). Zondek, B. and H. Kron, Klin. Wchnschr. **11**: 849. 1932.

Intermedin is extracted by the ½% acetic acid from the desiccated powder of the hypophysis first treated with acetone. In the anterior lobe there are 2,857 units per gram, in the central lobe there are 80,000 units per gram. Intermedin is only in the coat of the third ventricle, but not in the liquor. It is quite different from oxytocin and vasopressin. In another part of the organism they could not find a substance giving a positive phoxinus test.
—E. Kodicek.

The tolerance for insulin in cases with icterus (Die Insulintoleranz bei Fällen von Ikterus). Boller, R. and K. Uberrach, Klin. Wchnschr. **11**: 671. 1932.

In 17 cases of icterus of different etiology a high tolerance for insulin was found. The insulin tolerance test is parallel with the galactose test for liver insufficiency.—E. Kodicek.

The influence of denervation of the adrenals upon diabetes mellitus (Einfluss der Durchschneidung der Nebennieren auf den Diabetes Mellitus). Ciminata, A., Klin. Wchnschr. **23**: 150. 1932.

The pancreas was removed from two dogs which had been kept on a carbohydrate diet. After three days, when a definite diabetic condition had developed, the adrenals were denervated. The blood and urine sugar levels immediately fell. One dog survived from June 22, 1928, to Feb. 15, 1930. The author concludes that denervation of the adrenals lowers the blood sugar in diabetes; that in dogs life can continue after removal of the pancreas and denervation of the adrenals; and that it is only a matter of time and more extensive research before this method will find a practical appreication in diabetic cases in the human.—L. C. Wyman.

Muscular glycopexis after work and its relation to the innervation of the pancreas (La glycopexie musculaire après travail et ses rapports avec l'innervation du pancréas). Dubois, G., Arch. internat. de pharmacodyn. et de therapie, **41**: 65. 1931. Abst., Chem. Absts. **26**: 4846.

Insulin causes a resynthesis of the muscle glycogen consumed during work. Unless the bulbar center of the vagus and the vagus nerves themselves are intact, the insulin necessary for this resynthesis is not released by the pancreas. After section of the vagus, stimulation of the end of the left vagus alone provides for the resynthesis of the glycogen. Adrenaline sometimes prevents this resynthesis, and the muscle glycogen falls; after bilateral adrenalectomy, this adrenaline effect is no longer observed.

The tolerance for insulin (Ueber Insulintoleranz). Falta, W. and R. Boller, Klin. Wchnschr. **11**: 668. 1932.

The tolerance for insulin is the largest dose which just causes the hypoglycemic shock. In 12 normals, 4 patients with low fever and in 5 patients with obesity the authors found a normal tolerance of 75 units. Also in 3 cases of diabetes they found a normal tolerance.—E. Kodicek.

The action of insulin on the glycogen distribution in normal animals. Goldblatt, M. W., Biochem. J. **24**: 1198. 1931.

The increases in liver-glycogen observed to follow the injection of insulin into starving young rabbits cannot be explained by changes occurring in gly-

cogen and "free sugar" in other situations. This is considered the more important since the majority of experimental work tends to show that muscle-glycogen is irreversible and so cannot contribute to circulating carbohydrate. These accumulations of liver-glycogen are not associated with changes in blood constituents other than diminution in blood-sugar and blood-inorganic P. It is considered that under the described conditions glycogen formation from endogenous sources is definitely increased.—Author's Summary.

Hypertension and diabetes. John, H. J., Ann. Int. Med. **5**: 1462. 1932.

Blood pressure in non-diabetics rises proportionately higher in the case of obese individuals than in those of normal weight (approximately 12% increase). Reduction in weight in non-diabetics brings about reduction in blood pressure. The consensus of opinion of various authors is that the blood pressure is higher in diabetics than in normal individuals of the same age. In John's series of 1828 cases of diabetes, the blood pressure was the same as in normals below and including the fourth decade; above this age the incidence of high blood pressure was greater in diabetics. In 443 cases of diabetes associated with hyperthyroidism 37.6% of the patients had a blood pressure below 140 mm. and 62.4% above 140 mm. against 54.3 and 45.7%, respectively, in diabetes not associated with hyperthyroidism. Diabetics up to 30 years of age showed hypertension only in 9%, whereas in diabetics with hyperthyroidism, hypertension was present in 42% of this group of young individuals. Up to the fifth decade, hypertension in itself presents no marked incidence of diabetes; after the fifth decade the incidence rises markedly. In 50 cases of hypertension in the series, glycosuria was present in 36%. In 50 glucose tolerance tests on these individuals, 39% showed glycosuria in the presence of a normal curve and 55% showed no glycosuria in the presence of a diabetic curve. The renal threshold in cases of hypertension is high. A close relationship exists between hypertension and diabetes, and hypertension occurs more frequently in diabetics than in non-diabetics.—Author's Abst.

Influence of insulin after application of red and ultra-violet light (Beeinflussung des Insulins durch rote und ultraviolette Bestrahlung). Küstner, H. and W. Eissner, Klin. Wchnschr. **11**: 499. 1932.

The authors injected 10 rabbits with 0.6 units insulin per kgm. body weight. There was no difference between normal insulin and insulin after light application. Only after ultra-violet radiation they did not find as great a lowering of blood sugar as normal. The insulin 16 hours after application of the light was as efficacious as normally.—E. Kodicek.

Insulin in treatment of pernicious anemia. Lebedov, A. Y., Vrach. gaz. (No. 18). 1340 (Sept. 30). 1931. Abst., J. A. M. A. **97**: 1749.

Lebedov describes his observations in the treatment of seven persons with pernicious anemia. Insulin was used to increase the appetite; this treatment was followed by a decided improvement in the patient's condition. In instances in which arsenic and iron were ineffective, insulin produced an increase in the percentage of hemoglobin as well as an increase in the number of red blood cells and an improvement subjectively and objectively in the patient's condition. There was no influence on gastric secretion. In the cases in which the spleen was enlarged the treatment led to a decrease in its size. The effects of insulin lasted not only during but after the conclusion of treatment. Secondary anemia conditions were markedly improved; but in pernicious anemia and in anemia without regeneration of erythrocytes there was a relapse within six months after treatment.

The habitual rise of the blood sugar in inanition. Mischnayevski, M. N. and A. S. Voronoff, Medicinseaya Myssl. **6**: 1. 1931.

The author noted the fact that in dogs there was a customary rise in the blood sugar near the hours of feeding. This observation corresponds to the fact that there is a rise in leucocytes at the same time.—M. Breitmann.

Diabetes mellitus; colloidal osmotic pressure of the blood. Rabinowitch, I. M., Arch. Int. Med. **46**: 752. 1930.

Though this investigation failed so far as finding an explanation for certain high cholesterol values occasionally met with in diabetic blood is concerned, a new phenomenon was observed. It is suggested that though there is relatively little direct evidence, the sum of all available data (clinical and laboratory) tends to support the view that in diabetes with lipemia there is constantly exerted in the capillaries a colloidal pressure greater than the normal. To overcome the latter for purposes of renal excretion, a greater hydrostatic pressure is required; this increased pressure, though relatively small, when continued over a long period of time, probably has the same effect as more marked intracapillary pressure exerted over a short period of time. In animals the latter, when produced either by injection of epinephrine or by sympathetic stimulation, is alleged to cause arteriosclerosis. Is this, therefore, a cause of the marked incidence of cardiovascular disease in diabetes?

Concerning the influence of insulin on the intraocular pressure (Ueber die Einwirkung des Insulins auf den intraokularen Druck). Räihä, C. E. and L. Grönlund, Scandinav. Arch. f. Physiol. **62**: 70. 1931.

The authors tested the effect of intravenous injections of insulin on the intraocular pressure in 12 rabbits. They have observed a drop in the pressure, which was followed by a temporary rise and then a new drop which lasted for some time. The drop in the intraocular pressure is explained partially by the effect of the insulin on the cardiovascular system and partially by the other effects of insulin, which act similarly to the stimulation of the parasympathetic system. The rise in the pressure is caused by the increased function of the glands with sympathicotropic secretions, which is brought on by the insulin. The experiments are illustrated with charts.—A. Rudy.

The mechanism of action of insulin; information of ammonia in muscular activity of healthy and of diabetic individuals and the influence thereon of insulin (Beitrage zum Wirkungsmechanismus der Insulins; über die Ammoniakbildung bei Muskelarbeit des Gesunden und des Diabetickers und deren Beeinflussung durch Insulin). Schwarz, H. and M. Taubenhaus, Biochem. Ztschr. **236**: 474. 1931.

An increase of ammonia in the blood from the basal vein of an exercising arm was demonstrated. The increase was observed only in the working arm, the other arm giving control figures. The increase was constant after about six minutes' work and returned to normal after 15-20 minutes. The average change was from 0.05 mgm. per cent to 0.20 mgm. per cent. The diabetics showed the same change as non-diabetics. After giving insulin there was a smaller increase in ammonia after exercise, averaging about 50% less. If the insulin effect is neutralized by dextrose then exercise causes about the same increase as before giving insulin. The effect of insulin is stated to be due to an interference of the cleavage of adenylic acid to inosinic acid and ammonia. There is also a reduction of inorganic phosphorus after giving insulin due to changes in phosphocreatine.—J. M. Looney.

The mechanism of action of insulin; the ammonia content and the formation of ammonia in the liver and the influence of insulin on the same (Beitrage zum Wirkungsmechanismus des Insulins; über den Ammoniakgehalt und die Ammoniabildung der Leber und deren Beeinflussung durch Insulin). Schwarz, H. and M. Tauberhaus, Biochem. Ztschr. **239**: 201. 1931.

The ammonia content of the livers of white mice was investigated before and after giving insulin. The livers of 20 gm. white mice killed by decapitation were placed in a freezing mixture of carbondioxide, snow and ether. The NH_3 content was determined by rubbing with saturated borax solution, and the ammonia formation by rubbing in tyrode solution. A distinct decrease in the ammonia N content of the livers of the insulinized animals was noted, the average for 19 controls being 3.72 mgm. per 100 gms. of liver, and for 20 insulinized animals being 2.38 mgm. After rubbing in tyrode solution the livers from both controls and treated animals showed an appreciable increase in NH_3-N but no significant difference in the two values; that for the controls being 9.64 mgm. per cent and for the insulinized animals being 9.70 mgm.

per cent. There was found no relationship between the glycogen content and the amount of ammonia. The increase in ammonia is stated not to be due to changes in urea, but is probably due to deaminization of amino acids and purins.—J. M. Looney.

Diet and diabetes. Simpson, V. E., South. M. J. **25**: 489. 1932.

Tables and case histories illustrate the author's general principles that the diabetic should have as nearly a normal diet as possible. The use of extremes in diet and of so-called diabetic foods is discouraged.—J. C. D.

Treatment of older diabetic patients with cardiovascular disease. Strouse, S., S. Soskin, L. N. Katz and S. H. Rubinfeld, J. A. M. A. **98**: 1703. 1932.

Both clinical and experimental evidence indicates the increasing incidence of arteriosclerosis and disease of the heart in diabetes. Insulin itself has been accused of being responsible for some of the cardiac deaths in diabetes. The question of proper therapy of the diabetic patient with cardiovascular disease has not received sufficient study. Seven patients were treated with diabetes with clinical evidence of coronary sclerosis or angina pectoris. All patients were under close observation in the metabolic unit of the Michael Reese Hospital. Each patient was kept on his accustomed diet for from two to four weeks. This period was followed by a similar one in which the diet was unchanged but insulin was used in therapeutic doses. In addition, on each patient an acute experiment, studying the effect of one large dose of insulin, was made. The results of both acute and chronic experiments, based on both objective and subjective evidence, indicated a definite deleterious effect of insulin on the heart, whether an insulin hypoglycemia had been produced or whether it had been used in therapeutic doses. One patient on whom it was not necessary to use insulin showed the same effect with a low carbohydrate diet. As a result it was concluded that the needs of the impaired myocardium must not be forgotten in the effort to control the metabolic manifestations of diabetes. The impaired myocardium apparently needs available glucose.—S. Strouse.

The relation of parathyroidectomy to estrus, pregnancy, and lactation in the albino rat. Chandler, S. B., Anat. Rec. **53**: 105. 1932.

Experiments were made to determine the effects of estrus, pregnancy, and lactation on the parathyroidectomized albino rat. One hundred and forty matings were made. All females were operated and about one-half of the males. Some operations were done before puberty, some after puberty, and some following the birth of a normal litter. After mating, the female genitalia were observed to determine the approximate time of insemination, since copulation produces considerable irritation of the vaginal orifice. This sign furnished a reliable criterion by which the age of embryos was determined. If the estrous period made any change in the susceptibility of the parathyroidectomized rat to tetany, it was so slight that it could not be detected. Operated females became pregnant as regularly as the normal controls. All females that suckled more than four to six young suffered from marked nutritional changes, especially of the incisor teeth. Tetany was very marked in those mothers nursing large litters. An infection persisted in the eyes and nares of all. The intensity and number of symptoms increased as the lactation period advanced. One female died during lactation. Pregnancy caused the most marked symptoms, with death in 12 cases out of a total of 39. Emptying the uterus relieved pregnant females that were so ill as to require practically no anesthetic. These moribund animals recovered as quickly as normals subjected to an abdominal operation.—Author's Abst.

The sites of decalcification and of bone lesions in experimental hyperparathyroidism. Jaffe, H. L., A. Bodansky and J. E. Blair, Arch. Path. **12**: 715. 1931.

From a study of the bones of guinea-pigs with experimental hyperparathyroidism it is concluded that the rate of decalcification of the bony skeleton at any site is related to the rate of bone growth and metabolic lesions are more prominent in experimental hyperparathyroidism in regions of normally active growth of bone and less prominent in regions of less active growth. In the latter, simple thinning of the bone is sometimes the only change observed.

This conception makes intelligible the greater susceptibility of young animals to parathyroid extract and the reported details of the changes in the different bones and in the various portions of certain bones in experimental hyperparathyroidism.—H. L. Jaffe.

Effect of parathyroid operations on calcium in man (De l'influence des opérations parathyroïdiennes sur la calcémie chez l'homme). Jung, A. and A. C. Hakki, Compt. rend. Soc. de biol. **108**: 40. 1931.

Removal or damage to one parathyroid results in the reduction of hypercalcemia to normal level. If the blood calcium is normal at the time of operation, there is little or no reduction. This is based on several cases of polyarthritis ankylosa and scleroderma with high calcium and on partial thyroidectomies.—J. C. D.

Parathyroid hormone eosinophilia in children with diphtheria (Die Parathormoneeosiniphilie diphtheriekranker Kinder). Lenhart, G. and E. V. Lederer, Arch. f. Kinderh. **93**: 55. 1931.

Healthy children show five hours after the injection of parathormone a diminution in eosinophiles. In children sick with diphtheria, there is an increase, but this also returns to the initial levels in 24 hours. This action speaks for a toxic effect of diphtheria on the cells of the parathyroid gland. —M. B. G.

The parathyroid hormone eosinophilia of healthy and exudative nurslings (Die Parathormoneosinophilie gesunder und exsudativer Sauglinge). Lenart, G. and E. V. Lederer, Arch. f. Kinderh. **93**: 181. 1931.

The authors in a previous communication showed that the injection of 1 unit of parathormone (Lily) per kgm. of body weight diminished the eosinophile count in the 5th hour after the injection. The previous number of eosinophiles were restored in 24 hours. In the present series they injected 10 units instead of the above dose into children with an exudative diathesis between the ages of 3 to 12 months. The latter were chosen because of the probable relationship between this condition and the parathyroid glands on the basis of calcium content of blood, water metabolism and eosinophilia. Parathyroid curves in both normal and exudative children may be divided into two main groups, and two subdivisions: 1. Decrease and then return to initial values in 24 hours. (a) In older children, 6 hours after the injection of parathormone there is a marked reduction with a return to initial values in 24 hours. (b) There is a fall in values 6 hours later but there is a rise in 12 hours which is above the original figure and then a subsequent return to initial values in 24 hours. 2. Prolonged action with a return to initial figures in 47 to 72 hours. (a) A prolonged instead of a short course consisting of a drop, slight rise, slight drop, then a gradual rise to normal. (b) Two or more peaks following fall. Exudative children show Type 2 (b).—M. B. G.

Studies on cerebrospinal fluid and serum calcium, with special reference to the parathyroid hormone. Morgulis, S. and A. M. Perley, J. Biol. Clin. **88**: 169. 1930.

The relation of cerebrospinal fluid calcium to the calcium of serum has been investigated in man and in the dog. It was found that in experimental jaundice there was no change either in the serum or in the cerebrospinal fluid calcium. The ingestion of calcium salts caused only a small rise in the serum calcium without materially affecting the calcium of the cerebrospinal fluid. If the feeding of calcium was accompanied by injections of parathyroid hormone the serum calcium was raised considerably and beyond the response of the cerebrospinal fluid calcium. Similarly when the serum calcium was greatly increased by means of a continuous intravenous injection of a modified Ringer solution containing a very large amount of $CaCl_2$, the cerebrospinal fluid calcium remained relatively low, and only in a few instances did it undergo a large absolute increase. This tendency of the cerebrospinal fluid calcium to maintain its level within narrow limits suggests that perhaps other factor besides those of the membrane equilibrium are operative in regulating it. The parathyroid hormone apparently has no effect on the distribution of the calcium between

serum and cerebrospinal fluid because the changes upon intravenous injection of calcium were the same both in normal and parathyroidectomized animals at the time the latter have developed tetany. The transfer of calcium to the red cells following parathyroidectomy, and the existence of a slowly dissociable organic calcium compound in serum are discussed and reasons are given for denying both. By dialyzing serum against cerebrospinal fluid, an attempt has been made to throw light upon the problem of the quantitative relationship between the two calcium compounds, namely, the diffusible inorganic and the non-diffusible organic, and whether the formation of the latter is governed by the parathyroid hormone. These dialyses were made under normal conditions and after continuous injection of massive doses of calcium chloride, with or without the addition of parathormone, also on parathyroidectomized or on unoperated dogs. The evidence obtained from these experiments tends to show that the parathyroid hormone does not have any effect upon the distribution of the calcium of serum and cerebrospinal fluid.—Authors' Summary.

Condition simulating human scleroderma in rats injected with parathyroid hormone. Selye, H., J. A. M. A. **99**: 108. 1932. Abst., A. M. A.

In the course of the collection of experimental data on rats injected with parathyroid hormone, the author noted that young suckling rats receiving in some cases only a single injection of 5 units of parathyroid extract intraperitoneally develop within some days a specific skin disease. This condition presents itself first as a hardening of the skin on the back, extending bilaterally from the head to the lower border of the ribs. Within two or three days the hair over these areas begins to fall out and concomitant with this prenomena the skin becomes harder and thicker. Ulceration of these symmetrically arranged affected areas takes place in some parts, and finally after healing a bare, hairless, atrophic skin results. This condition in rats possesses striking points of similarity with the human disease known as scleroderma and sclerodactylia, in which condition there occurs a connective tissue hyperthophy in the skin, likewise mostly in symmetrical distribution, together with degeneration of this hypertrophied connective tissue and ulceration of the affected areas. Finally healing results in the atrophic skin over these areas. The author's report offers further substantiation for the concept that hyperparathyroidism is related to scleroderma.

On the physiology of the parathyroid glands (Zur Physiologie der Nebenschilddrüsen). Speranskaja-Stepanowa, E., Ztschr. f. d. ges. exper. Med. **79**: 523. 1931.

The author reports observations indicating a temporary rise in the blood calcium during the first few hours after parathyroidectomy. As a similar temporary rise was seen after adrenalectomy during the period when an increased tonus of the sympathetic system was presumed to be present and as sympathetic stimulation produced a rise in blood calcium, he concludes that normally the parathyroids have an inhibitory action on the sympathetic system in addition to holding up the level of the blood calcium. He also reports observations that stimulation of cervical sympathetic branches produces a hypercalcemia indicating that the parathyroids receive sympathetic innervation from this source.—C. A. Dragstedt.

Congenital bone dysplasia (osteogenesis imperfecta) associated with lesions of the parathyroid glands. Wyatt, T. C. and T. H. McEachern, Am. J. Dis. Child. **43**: 403. 1932.

A case is described in a 4½-weeks-old infant in which there was a marked congenital bone dysplasia and unusual vascularity of the parathyroid glands with a relatively small amount of parenchymal tissue. A brief review of osteogenesis imperfecta and the relation of the parathyroid glands to disease of bone is given. The possibility is suggested that so-called "osteogenesis imperfecta" may sometimes be based in part on a congenital parathyroid disturbance rather than be purely the result of faulty mesoblastic differentiation.

—M. B. G.

Effect of splenectomy on the susceptibility of the thymus to karyolytic agents (Influence de la splénectomie sur la sensibilité du thymus aux agents caryoclasiques). Dustin, A. P. and S. Zylberszac, Compt. rend. Soc. de biol. **108**: 1162. 1931.

In normal mice, injections of trypaflavine produce lysis in the cortex of the thymus and in lymphoid tissue in other parts of the body. After splenectomy the thymic cells become resistant to this poison but the germinal centers of the lymphatic system remain as susceptible as before splenectomy. This suggests that the cells of the cortex of the thymus are not identical with those of the lymphatic system.—J. C. D.

The basis of our knowledge of so-called status thymo-lymphaticus (Über die Grundlagen der Lehre des sog. Status thymico-lymphaticus). Hammar, J. A., Acta paedia. **11**: 241. 1930.

Upon the basis of the study of the thymus gland of 337 persons who died suddenly and accidentally, Hammar concludes that the anatomical foundation for the theory of status thymolymphaticus is based upon false premises. The existence of a hyperplasia of this system must be considered from the viewpoint of a secondary and not from a primary effect. The lymphocytic relationship between the thymus, glandular tissue and the blood appears to be under the influence of some general influence which may be incretory in character. This incretory influence may be partly depressor and partly excitor in nature. The weakening of the first and the strengthening of the second element results in an increase in the lymphocytes, at least in the thymus, with a corresponding thymic hyperplasia. The latter may also be present following castration or in Basedow's disease and is evidently linked up with a general idiosyncrasy. This latter should not be considered as being due to the thymic hyperplasia but to the underlying primary causes. In so-called mors thymica (the nature of which we do not know) the thymus in the majority of instances is normal in size and is hyperplastic only in exceptional cases.—M. B. G.

A primary carcinoma of the thymus and its histogenesis (Primäre Carcinome der Thymusdrüse und ihre Histogenese). Parabutschew, A., Ztschr. f. Krebforsch. **30**: 380. 1929.

In four cases reported the carcinomas derived from the reticulum and were partly small celled and partly like epidermis. The gonad function was lowered. Such cases represent a transition from benign to malignant tumors. —M. Breitmann.

Thymoma (Thymon). Stefko, W. and S. Kolesnikowa, Ztschr. f. Krebforsch. **31**: 155. 1930.

A malignant tumor (thymoma) which passed over the heart and left lung was noted in a man 53 years old. The thyroid showed enlarged proliferating follicles and in the adrenal the medullar substance was replaced by a loose fibrous tissue.—M. Breitmann.

Sedimentation of blood corpuscles in hyperthyroidism (La eritrosedimentación en los hipertiroideos). Castex, M. R. and M. Schteingart, Rev. Soc. argent. de biol. **7**: 487. 1931.

A normal velocity appeared in 16 cases, accelerated in 12 and retarded in 2. There was no strict relationship to the basal metabolism or symptoms. In severe cases accelerated sedimentation is more frequent.—J. T. Lewis.

Sedimentation of the erythrocytes in hyperthyroid cases (L'érythrosédimentation chez les hyperthyroïdiens). Castex, M. R. and M. Schteingart, Compt. rend. Soc. de biol. **109**: 327. 1932.

In 30 hyperthyroid cases, sedimentation time was normal in 16, accelerated in 12, and retarded in 2. There was no relation between sedimentation time and severity of disease.—J. C. D.

Thyroid stimulating action of blood serum (Hipófisis y tiroides; poder excito-tiroideo del suero sanguíneo). del Castillo, E. B. and A. Magdalena, Rev. Soc. argent. de biol. **7**: 458. 1931.

Blood serum of normal, hypophysectomized and thyroidectomized dogs, of patients with hyperthyroidism, acromegaly, amenorrhea, and of normal human subjects was injected into guinea pigs of less than 200 gm. weight and their thyroids examined microscopically (Aron's test). The results were irregular; a positive reaction (hyperactivity) was observed in guinea pigs submitted to no treatment or simply injected with saline. Aron's test was not confirmed.
—J. T. Lewis.

End-results of surgery in exophthalmic goiter. Clute, H. M. and J. R. Veal, J. A. M. A. **99**: 642. 1932. Abst., A. M. A.

The authors point out that the immediate advantages of surgical measures in the treatment of exophthalmic goiter have been convincingly demonstrated and that the operation of subtotal thyroidectomy has been made a safe procedure. They summarize the results of surgical treatment in 97 patients whom they have followed consistently for over five years since operation and have checked by personal examination and basal metabolic estimations. In 82 patients complete and satisfactory cure was obtained. In seven other patients slight toxicity is still present, entirely controlled by either secondary operation or compound solution of iodine. In three patients of the group myxedema developed; this was entirely controlled by desiccated thyroid. Four of the patients in the group are still toxic. None of the four are in any way incapacitated, and all are working. One of the patients in the group died following a recent secondary operation for recurrent hyperthyroidism and congestive heart failure. It is, therefore, the authors' belief that 92, or 94.8%, of these 97 patients are cured of their disease by subtotal thyroidectomy, and that this figure may be assumed to be a fair estimate of the probability of cure of exophthalmic goiter by adequate surgical measures.

The production of hyperplasia of the thyroid gland by chemical means with special reference to purine bases, their derivatives and amino acids. Cole, W. H., N. A. Womack and C. S. Stone, Jr. Proceedings of Central Society for Clinical Research, November 22, 1929. Abst., J. Clin. Investigation, **8**: 672. 1930.

In attempting to explain the effect of certain infections and toxemias on the thyroid (hyperplasia, desquamation, loss of colloid and iodine content) which the authors and others have observed, certain noteworthy facts were encountered. The methylpurines, caffeine and theophylline will produce a hyperplasia of the thyroid cells on certain occasions, which is almost indistinguishable from the hyperplasia seen in the toxic goiters of human beings. It is felt that since these drugs are so similar to the products of protein catabolism (specially those of nucleoproteins) the effect may be dependent upon toxic by-products formed during protein destruction. The thyroid of an animal which had received an amino acid, tyrosine, in doses insufficient to produce toxic effect showed a marked degree of desquamation and loss of colloid. It must be admitted and emphasized that the results obtained from the administration of most of the drugs used in this series are subject to correction since many of the drugs were used on only one or two occasions. The authors feel, however, that the production of a marked degree of hyperplasia following administration of certain drugs is significant, even though it does not occur in every instance. As a whole, inorganic drugs apparently do not produce many changes in the thyroid of animals even after administration of fatal doses. The results contained in this report are preliminary. Further investigation is being done on the effects of drugs, especially by-products of protein destruction, upon the thyroid gland of animals.

Acid base equilibrium in diseases of the thyroid (L'equilibre acido-basique dans les maladies de la glande thyroide). Coelho, E., Rev. franç. d'endocrinol. **9**: 376. 1931.

In the most of the cases of Basedow's disease the alkaline reserve was not diminished. The author, therefore, does not believe that this disease is characterized by a state of acidosis, as some authors contend. In case of coma in Basedow's disease there is strong acidosis. The acid-base equilibrium is inde-

pendent of the increase in the basal metabolism. The author does not consider the measure of alkaline reserve as proof of a diagnosis of hyprthyroidism. After sub-total thyroidectomy there is no tendency to alkalosis nor, in general, to normalization of the acid-base equilibrium in those patients who show acidosis before operation. In hypothyroidism and myxedema the authors found variations in alkaline reserve similar to those of hyperthyroidism..

—Author's Summary (Translated).

Hyperthyroidism in children; review of fifty-seven cases. Dinsmore, R. S., J. A. M. A. **99**: 636. 1932. Abst., A. M. A.

During the past few years the author and his associates have seen at the Cleveland Clinic a number of cases of hyperthyroidism in children. Although formerly it was thought that hyperthyroidism in children under 14 years of age occurred but rarely, their experience has led them to believe that this disease is not as uncommon as is generally supposed. The diagnosis of hyperthyroidism in a child is not difficult in most instances; as a matter of fact, these patients frequently come to the physician with the diagnosis already made and, in the typical case, even the casual observer can identify the disease. Among the most common symptoms are tachycardia, exophthalmos, enlargement of the thyroid gland, extreme nervousness, easy excitability, great irritability and the tendency to cry over the most trivial circumstances. The author's experience with estimations of the basal metabolism in children with hyperthyroidism has been generally unsatisfactory. In the first place, it is difficult to know that a child is in a true basal condition; secondly, there are such variations in the estimations of the basal metabolism determined by different standards that it usually appears that the standards available are not sufficiently accurate. His tests have shown wide variation, especially from the initial reading. Formerly it was the practice to perform ligations in these cases and to send the child home for a period of three months, but in the author's latest series it has been possible to do lobectomy or thyroidectomy in practically every case. It must be remembered that for some reason the improvement that follows ligations is very definite. In children this improvement is greater than that seen in the average adult. Therefore, this procedure should not be discarded in favor of lobectomy if there is any doubt as to the wisdom of the latter as the primary operation.

Fluorine treatment of exophthalmic goiter and hyperthyroidism (Traitement de la maladie de Basedow et de l'hyperthyroïdisme par le fluor). Goldemberg, L., Presse méd. **38**: 1751. 1930.

Since 1928 the author has experimented with sodium fluoride in treatment of hyperthyroidism. He gives it in aqueous solution of 2 to 100 orally in doses of 10 drops 4 times a day in a little milk. A very small number of patients tolerated this dosage for more than a month. Most of them presented nausea occasionally followed by vomiting and diarrhea with or without intestinal colic. Hence, the author resorted to intravenous injections of sodium fluoride. Goldemberg concludes that fluorine treatment can improve and even effect clinical cure in sufferers from exophthalmic goiter; that simple hyperthyroidism could quickly be controlled by fluorine treatment alone, especially if employed orally; and that fluorine therapy by mouth is much more effective than when given intravenously. In case of exophthalmic goiter or of simple hyperthyroidism he begins with sodium fluoride orally and in the event of gastrointestinal intolerance he resorts to ammonium fluoride orally in association with intravenous injections of sodium fluoride in sterilized aqueous solutions of 2 to 100 in doses of 4 to 5 cm. every other day in series of 15 injections with intervals of rest of 15 or 20 days between one and the next series. Fluorine treatment by mouth must be continued for several months until the metabolic rate reaches normal. Goldemberg believes that intravenous injections of fluorine in doses he indicates are completely devoid of dangers.—I. B.

The effect of the thyroid gland on the pigmentation of the hair coats of rabbits and a Siamese cat. Il'in, N. A., Züchtungskunde, **6**: 304. 1931. Abst., Chem. Absts. **26**: 4844.

The result of forced feeding of thyroid tablets on the pigmentation of rabbits depended on the external temperature. At 0° or lower there was little

or no effect; at about 18-21°, depigmentation occurred. Intermediate temperatures produced partial depigmentation. After thyroidectomy, the new hair was darker; in the Siamese cat, the hair changed from cream-colored to chocolate-colored. Thyroidectomy causes a rise in the stimulus threshold for pigmentation and produces a result opposed to the hyperthyroid condition.

Hyperthyroidism showing carbohydrate metabolism disturbances. John, H. J., J. A. M. A. **99**: 620. 1932.

The present study comprises clinical and laboratory observations made over a period of ten years, including an intensive study made during the period from Jan. 1, 1925, to Oct. 1, 1931. During this time, about 9,000 cases of thyroid disease have been seen in the Cleveland Clinic, most of which were cases of hyperthyroidism (exophthalmic goiter, adenoma with hyperthyroidism). Of this group, 620 cases, or 6.88%, showed some degree of non-physiologic hyperglycemia (fasting or two and one-half hours or more postprandial) either with or without glycosuria. During these years it has been the practice to make a routine blood sugar estimation in every new case, as this gave much information about many unsuspected cases of diabetes which would not have been picked up otherwise. Most of the cases, which showed some degree of non-physiologic hyperglycemia, were then followed up and studied further for a period up to ten years. When the 620 cases showing non-physiologic hyperglycemia were followed up further, it was found that in some the hyperglycemia was present in only the primary examination and that in others the hyperglycemia disappeared without any medication. Consequently, these cases are not included in consideration. In some other cases the patients have not been observed for a long enough period to be included in this series. In some cases inadequate data were available, and for that reason they are not included. Intensive observations over a period of from one to ten years were made on 166 cases which alone are included in this special study. All of these showed a definite disturbance of carbohydrate metabolism. By a very conservative estimate, however, I should say that about 200 cases showed what might be called definite hyperglycemia like that of diabetes. In some of these cases the hyperglycemia was purely functional in type and therefore disappeared in a few weeks or months after thyroidectomy on dietary treatment alone or combined with insulin, but—as further experience taught—the hyperglycemia would not have disappeared in all cases without such treatment. In the total of 620 cases, of hyperthyroidism in which hyperglycemia was present, it remained in 30% and disappeared in 70%, a figure that is close to the average incidence of diabetes in cases of hyperthyroidism as reported in the literature (2.3%). Thus, of this series approximately 200 patients remained diabetic and had to be treated as such, and 35.7% of them are still taking insulin in order to control the diabetic state. An analysis was made of the 166 cases in this series in order to show the progress of the patients. After thyroidectomy 55% of the patients improved as far as their diabetic status was concerned; in 15% the diabetic condition remained stationary, and in 30% the patients either required more insulin or, if not taking insulin, it is but a question of time until insulin will have to be administered. As stated, 35.7% of the entire group are still taking insulin.—Author's Abst.

The thyroid and metabolism during exercise (Schilddrüse und Arbeitsstoffwechsel). Kommerell, B., Arch. f. d. ges. Physiol. **227**: 1. 1931.

In dogs the amount of work was measured by means of a treadmill and the respiratory exchange during the work studied by the Douglas bag method. The kind of food has no effect on the oxygen consumption. In a protein diet there was a fall in the respiratory quotient which was explained by the utilization of fat due to the lack of carbohydrate reserve. In the work done after the ingestion of food, the specific dynamic effect is added to the metabolism produced by the exercise. Removal of the thyroids causes a small fall in metabolism during exercise. This fall can be prevented by the administration of thyroid extract. The muscular efficiency was not altered by thyroxin. The increase in metabolism due to the thyroid is produced by a central nervous action rather than an increased cellular activity.—E. L.

Demonstration of thyroid hormone in muscle (Über den Nachweis von Schilddrüsenhormon in der Muskulatur). Kommerell, B., Arch f. exper. Path. u. Pharmakol. **161:** 141. 1931. Abst., Physiol. Absts. **17:** 56.

Thyroidectomized dogs fed on a meat-free diet show a further fall of 18 to 20% in basal metabolism. A meat diet causes a rise in basal metabolism if the meat comes from normal animals, but no rise if it comes from thyroidectomized animals. The author concludes that normal muscle contains traces of thyroid hormone.

Specific dynamic action of food. II. Specific dynamic action of meat protein in alterations of thyroid function (Studien zur spezifisch—dynamischen Nahrungswirkung; II Mitteilung. Die spezifisch—dynamische Fleischeiweisswirkung bei Veranderungen der Schilddrüsenfunktion). Krauss, E., G. Bruni and R. Rettig, Ztschr. f. klin. Med. **112:** 19. 1929.

Tests of the increase in oxidation produced by administration of normal thyroid and of thyroid from cases of Basedow's disease show that there is no accumulation of the thyroid hormone in Basedow's disease but rather a decrease. Thyroidin (Merk) administered to healthy men, causes, in addition to an increase in basal metabolism, a rise in the specific-dynamic action of meat proteins. This increase in specific dynamic action through thyroid administration reveals a new reason for the reducing action of thyroid, which, however, is not as constant as is the increase in the basal metabolism. In frank Basedow's disease there appears, during the time of the determination after meat protein administration, an increase in oxidation greater than normal. This increase is great enough to account for two-thirds of the calories administered. The increase in heat given off is not due entirely to protein but also to fat. The percentage of increase over the basal rate is not greater in Basedow patients than in healthy subjects. The increase of the specific dynamic action of protein results from the long duration of the effect, which extends more than 9 hours and still does not return to normal. This makes it impossible to give the absolute values of the specific dynamic action of protein for Basedow's disease as is done for normal conditions. Meat, however, leaves the stomach in normal time in Basedow's disease. In the course of the authors' experiment the axillary temperature often rose to 37.5° C., the respiration quotient generally sank, acetonuria appeared together with a pronounced shifting of the pH of the urine to the acid side. Basedow's disease that has been improved by therapy can show an abnormal specific-dynamic action from protein and at the same time a normal basal metabolic rate. In nodular goiter with thyrotoxic symptoms in which the basal metabolism was increased about 20%, the specific-dynamic action of protein was normal. After thyroidectomy there was found an inclination to abnormal fat deposition associated with a normal resting metabolism and a lowered specific-dynamic action of proteins. Alterations in the energy expenditure used to produce increases in the specific-dynamic action of proteins when the basal metabolism is normal are assumed to be of greatest importance to the problem of endogenous emaciation and endogenous obesity. The basal metabolism in a case of Basedow's disease decreased to plus 17% after administration of Lugol's solution; the specific-dynamic action of protein decreased without exception, as it also did in 2 cases of untreated myxedema. The respiratory quotient scarcely changed during the course of the experiment. There was no acetone in the urine. Stomach emptying was normal. The axillary temperature in the cases of myxedema increased to 37.3° C. in the first 4 hours after meat administration. The extra heat production after meat administration could be assigned entirely to the protein in myxedematous as it is in normal cases. The basal requirement for protein in myxedema is lower than normal if determined from the kilograms of body weight, but normal if determined on the basis of square meters of body surface.—I. B.

The effect of thyroid substances on the larvae of Bufo viridis (Der Einfluss thyreoidaler Substanzen auf Larven von Bufo viridis und die Bedeutung dieser Stoffe für die Entwicklung des Keimdrüse bis zur Metamorphose). Krichel, W., Zool. Jahrb. **48:** 589. 1930. Abst., Physiol. Absts. **17:** 57.

Thyrade (Knoll) has a more marked accelerating action on the metamorphosis of larvae of the Bufo viridis than Novothyrol (Merck). In normal metamorphosis the external stage of development of the hind-limb buds always corresponds to the proliferation of the gonadic cords in the sex glands. The

animals treated with thyroid show an acceleration in the development of the gonads similar to that observed in the development of the body. There is a strict correspondence between the development of the gonadic cords and the limb buds in the animals treated with thyroid (whatever the preparation and concentration used). At the time of the external metamorphosis the cranial part of the gonad (future organ of Bidder) is already present in the normal animal. Larval ovogenesis is observed in the treated animals when the external stage corresponding to larval ovogenesis is observed in the treated animals when the external stage corresponding to larval ovogenesis in untreated animals is reached.

The influence of coitus and pregnancy on the colloid content of the thyroid glands of rabbits (Die Schilddrüsenkolloidveränderung bei Kaninchen unter dem Einfluss des Koitus und der Schwangerschaft). Krjlow, L. H. and A. J. Sternberg, Endokrinologie, **10**: 37. 1932.

Immediately after coitus there was a definite increase of weight and hyperaemia of the thyroid gland of the rabbit, accompanied by a marked decrease in the colloid content of the thyroid follicles. However, the colloid was restored during course of pregnancy, and near the end of pregnancy the amount present was frequently greater than that found in the non-pregnant female. The restoration of colloid was more rapid, however, if the animal failed to become pregnant after coitus. Coitus during pregnancy was also followed by a marked decrease in the colloid content. It was also found that 24 hours after delivery there was a less noticeable decrease in the colloid, independent of coitus. It was concluded that the colloid decrease was effected by coitus rather than the condition of pregnancy. The markedly dilated capillaries of the gland contained a homogeneous mass which superficially resembled the colloid found in the thyroid follicles.—J. M. Wolfe.

Cytological and metabolic investigations of human thyroid glands. Krogh, M., A. L. Lindberg and H. Okkels, Skandinav. Arch. f. Physiol. **63**: 92. 1931. Abst., Physiol. Absts. **16**: 628.

A series of surgically removed glands from cases of simple goiter and exophthalmic goiter with and without iodine treatment were examined. In exophthalmic goiter there was proliferation, cellular hyperactivity, and lack of storage of secretion; in cases previously treated with iodine greater formation of colloid was found than in untreated cases, but cellular hyperactivity was practically unaltered. Fed in suitable amount to adult male guinea-pigs, the simple goiter glands caused a greater increase in metabolism than did those from exophthalmic cases.

The effect of infections on the structure of the thyroid gland (Über den Einfluss von Infektionen auf den Bau der Schilddrüse). Leffman, A., Endokrinologie, **10**: 43. 1932.

The author briefly notes the results obtained by previous workers on this subject. His own contribution consists of an analysis of the structure of the thyroid gland in 349 autopsies of patients dying of various types of infections. Loss of colloid, desquamation of cells, fibrosis and hyperemia were noted in varying degrees. This apparently represented a general reaction on the part of the thyroid to infection. No particular type of reaction to any specific disease was noted, although the duration and severity of the infection seemed to play some part.—N. A. Womack.

Response of explanted cardiac muscle to thyroxine. Markowitz, C. and W. M. Yater, Am. J. Physiol. **100**: 162. 1932.

A study was made of the action of thyroxine on cultures of pulsating fragments of heart muscle removed from two-day-old chick embryos, before the appearance of nerve elements. Thyroxine exerted its typical effect on the frequency of pulsation and contractility of such fragments, bringing about a progressively greater increase in rate ending in some cases in fibrillation and paralysis. These results constitute evidence that in clinical hyperthyroidism the tachycardia is due to the action of thyroxine directly on the myocardium and not on intervening nerve elements.—Authors' Abst.

The theory of the thyroid effect (Zur Theorie der Schilddrusenwirkungen). Meyer, H. H., Deutsche med. Wchnschr. **57**: 1531. 1931.

The author's experiments show a real effect of thyroid hormone on the central system besides an influence of the thyroxine on the tissues, which causes an increased reactibility to a normal nervous stimulus. Cases of one-sided exophthalmos can only be explained by a central influence of the thyroxine.—E. Kodicek.

Hyperthyroidism in children under 10 years of age. Miller, H. C., Nebraska M. J. **15**: 363. 1930.

The author reports 3 cases following acute infections and one of exophthalmos. All 3 recovered, but one was operated upon for goiter.—M. B. G.

Thyroid tolerance in healthy children (Zur Thyreodintolerance gesunder Kinder). Rupilius, K., Arch. f. Kinderh. **93**: 116. 1931.

Thyreosan, a thyroid albumin preparation, was administered for periods of 2 to 6 weeks in doses up to 4 gm. of fresh thyroid substance to healthy children between one and 14 years of age. There was no influence on pulse rate, intestinal function, appetite or weight curve. Hyperthyroidism was not produced by large doses. Untoward results disappeared on discontinuance of the drug which were produced in a non-thyroid backward child and in three Mongolian imbeciles. Since the extract is harmless in normal children, the author considers that the latter effect shows perhaps a thyroid disturbance in these conditions.—M. B. G.

Ossification of the skeleton of the hand. III. Physiological osteoporosis. IV. Pathological forms. Hyperthyroid osteoporosis. The seasonal fluctuation of osteoporosis. Injurious effect of winter. Chronic conditions (Ossifications studien am Handskelet des Kindes. II. Die physiologische Osteroporose. IV. Pathologische Osteoporoseforman. Hyperthyroide Osteroporose. Die jahreszeitliche Schwankung der Osteoporose. Der "Winterschaden" chronische Osteoporosezustande). Stattner, E., Ztschr. f. Kinderh. **52**: 1; 14. 1931.

Osteoporosis of childhood may be a physiological condition due to destruction and rebuilding of bone which is dependent upon nutrition and growth. Pathological forms are the result of endogenous and exogenous factors such as heredity and intercurrent infections which produce a demineralization of bone. Rickets is not as important a factor as was formerly believed. Climate and seasonal variations may have an influence on osteoporosis similar to that on rickets and is evidenced in cases of chronic osteoporosis, one instance of which is cited. The author cites an instance of osteoporosis which he considers was due to the use of thyroid extract for three years. The child was mentally retarded and had a hypothyroidism and hypopituitarism.—M. B. G.

Comparison of exophthalmic goiter in Boston and Chicago, with especial reference to iodine reaction. Thompson, W. O. and J. H. Means, J. A. M. A. **99**: 1483. 1932. Abst., A. M. A.

In a comparison of exophthalmic goiter in Boston and Chicago, the authors found that: 1. The initial height of the basal metabolic rate is the same. 2. The reduction in basal metabolism during the administration of iodine is the same and occurs in the same length of time. 3. The minimum amount of iodine necessary to produce a maximum reduction in basal metabolism is probably about the same. 4. The sex ratio is approximately the same. 5. The age of onset is about the same. These observations suggest that the severity of exophthalmic goiter is the same in Chicago as it is in Boston. The severity of exophthalmic goiter, as judged by the average basal initial metabolism alone, does not seem to vary significantly in many clinics in different parts of the country.

The morphology and physiology of the salamander-thyroid gland; the effect of implantation of inorganic iodine upon the thyroid gland (Die Morphologie und Physiologie der Salamander-Schilddrüse. VI. Jodi-implantation und ihre Wirkung auf die Schilddrüse). Uhlenhuth, E. and C. Winter, Arch. f. Entwcklngsmechn. d. Organ. **119**: 516. 1929.

Iodine crystals were implanted into the peritoneal cavity of the larvae of Amblystoma tigrinum. Metamorphosis resulted at a size only half that at which the controls metamorphosed and as early as 9 days after implantation, while feeding iodine crystals had not produced precocious metamorphosis in previous experiments. The thyroids were greatly damaged by this procedure; in one case only 5 follicles were left, in another case only a mass of detritus was found at the site of the gland. The slow absorption of the iodine in the case of feeding does not produce such severe destruction and allows the iodine to be withheld in the thyroid, preventing it from acting upon the organism. In the case of implantation the iodine stays in the circulation after the breakdown of the thyroid activity, and produces precocious metamorphosis by acting upon the tissues of the animal.—Authors' Abst.

Iodine allergy and thyrotoxicosis (Jodallergie bei Thyreotoxikose). Wolfshon, G., Med. Klin. **27**: 1788. 1931.

The author describes his experiments with intradermal injections of 0.2 cc. potassium iodid. Patients with toxic goiter had a positive reaction of an intensely red macula, which reached its maximum in 10 minutes and then in an hour disappeared. Patients with non-thyrotoxic goiters had a negative reaction. The author recommends this test for practical use because of its ease and rapidity.—E. Kodicek.